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<b>(21) International Application Number:</b> PCT/US96/17324 <b>(22) International Filing Date:</b> 28 October 1996 (28.10.96)  <b>(30) Priority Data:</b> 60/007,126 31 October 1995 (31.10.95) US 9602857.6 13 February 1996 (13.02.96) GB  <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DE LASZLO, Stephen, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MANTLO, Nathan, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUBSTITUTED ARYL PYRROLES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE  <b>(57) Abstract</b>  The present invention addresses substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment. Cytokine mediated diseases refer to diseases or conditions in which excessive or unregulated production of one or more cytokines occurs. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines which are involved in immunoregulation and other physiological conditions, such as inflammation.		

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TITLE OF THE INVENTIONSUBSTITUTED ARYL PYRROLES, COMPOSITIONS CONTAINING  
SUCH COMPOUNDS AND METHODS OF USE5 BACKGROUND OF THE INVENTION

The present invention addresses 2, 5-substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment. Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production of one or more  
10 cytokines occurs. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines which are involved in immunoregulation and other physiological conditions, such as inflammation. IL-1, IL-6, IL-8 and TNF effect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived  
15 cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions.

Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions. [See, e.g., Dinarello et al.,  
20 Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

25 There are many disease states in which IL-1 is implicated. Included among these diseases are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, other acute or chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle  
30 degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic  $\beta$  cells.

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Excessive or unregulated TNF production has been implicated in mediating or exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, allograft rejections, fever and myalgias, due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

IL-6 is a cytokine effecting the immune system, hematopoiesis and acute phase reactions. It is produced by several mammalian cell types in response to agents such as IL-1 and is correlated with disease states such as angiofollicular lymphoid hyperplasia.

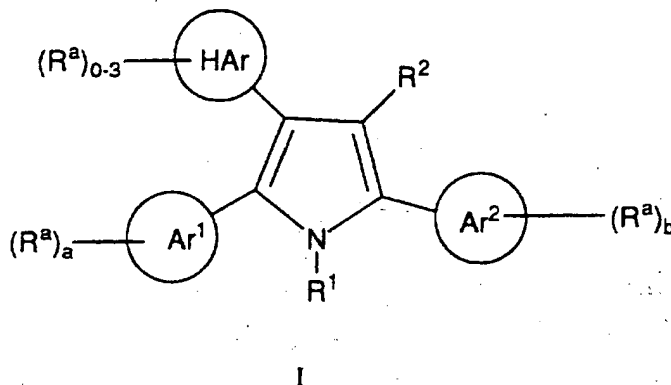
Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Like IL-1, IL-8 is produced by several cell types, including mononuclear cells, fibroblasts, endothelial cells and ketainocytes. Its production is induced by IL-1, TNF and by lipopolysaccharide (LPS). IL-8 stimulates a number of cellular functions in vitro. It is a chemoattractant for neutrophils, T-lymphocytes and basophils. It induces histamine release from basophils. It causes lysozomal enzyme release and respiratory burst from

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neutrophils, and it has been shown to increase the surface expression of Mac-1 (CD11b/CD 18) on neutrophils without de novo protein synthesis. There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e., compounds which are capable of inhibiting cytokines such as IL-1, IL-6, IL-8 and TNF.

### SUMMARY OF THE INVENTION

The present invention is directed to a compound represented by formula I:



wherein:

15  represents a 5-10 membered aryl group;

 represent a 5-10 membered aryl or heteroaryl group;

20 a and b represents integers, 0, 1, 2 or 3, such that the sum of a plus b is 1, 2, 3 or 4;

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represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1-3 R<sup>a</sup> groups;

5

each R<sup>a</sup> independently represents a member selected from the group consisting of: halo; CN, NO<sub>2</sub>, R<sup>21</sup>, OR<sup>23</sup>, SR<sup>23</sup>, S(O)R<sup>21</sup>, SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>C(NR<sup>20</sup>)NHR<sup>23</sup>, CO<sub>2</sub>R<sup>23</sup>, CONR<sup>20</sup>R<sup>23</sup>,  
 10 SO<sub>2</sub>NR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, OCONR<sup>20</sup>R<sup>23</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>20</sup>, C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup>, C(NR<sup>20</sup>)NR<sup>20</sup>R<sup>23</sup>, C(O)NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup> and tetrazol-5-yl;

15

R<sup>1</sup> is selected from the group consisting of: H, C<sub>1-15</sub> alkyl, C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, OR<sup>20</sup>, SR<sup>20</sup>, N(R<sup>20</sup>)<sub>2</sub>, S(O)R<sup>21</sup>, SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>23</sup>,  
 20 SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, N(R<sup>20</sup>)C(NR<sup>20</sup>)NHR<sup>20</sup>, CO<sub>2</sub>R<sup>20</sup>, CON(R<sup>20</sup>)<sub>2</sub>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, OCONR<sup>20</sup>R<sup>23</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup> and OCONR<sup>20</sup>R<sup>23</sup>;

25

R<sup>2</sup> is selected from the group consisting of: CN, S(O)R<sup>21</sup>, SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>N(R<sup>20</sup>)<sub>2</sub>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CON(R<sup>20</sup>)<sub>2</sub>, COR<sup>20</sup>, CO<sub>2</sub>R<sup>20</sup>, CONR<sup>20</sup>R<sup>23</sup>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup> and SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>;

30

R<sup>20</sup> represents a member selected from the group consisting of: H, C<sub>1-15</sub> alkyl, C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

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$R^{21}$  represents a member selected from the group consisting of:  $C_{1-15}$  alkyl,  $C_{3-15}$  alkenyl,  $C_{3-15}$  alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O),  $SO_2$  and  $NR^{20}$ , said alkyl, alkenyl, alkynyl, heterocyclyl, aryl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN,  $OR^{20}$ ,  $C(O)R^{20}$ ,  $O((CH_2)_nO)_mR^{20}$ ,  $NR^{20}((CH_2)_nO)_mR^{20}$  wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3;  $SR^{20}$ ,  $N(R^{20})_2$ ,  $S(O)R^{22}$ ,  $SO_2R^{22}$ ,  $SO_2N(R^{20})_2$ ,  $SO_2NR^{20}COR^{22}$ ,  $SO_2NR^{20}CON(R^{20})_2$ ,  $NR^{20}COR^{22}$ ,  $NR^{20}CO_2R^{22}$ ,  $NR^{20}CON(R^{20})_2$ ,  $NR^{22}C(NR^{22})NHR^{22}$ ,  $CO_2R^{20}$ ,  $CON(R^{20})_2$ ,  $CONR^{20}SO_2R^{22}$ ,  $NR^{20}SO_2R^{22}$ ,  $SO_2NR^{20}CO_2R^{22}$ ,  $OCONR^{20}SO_2R^{22}$ ,  $OC(O)R^{20}$ ,  $C(O)OCH_2OC(O)R^{20}$ ,  $OC(O)NR^{20}R^{23}$  and  $OCON(R^{20})_2$ ;

$R^{22}$  is selected from the group consisting of:  $C_{1-15}$  alkyl,  $C_{3-15}$  alkenyl,  $C_{3-15}$  alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

$R^{23}$  is  $R^{21}$  or H;

$R^{24}$  is selected from  $COR^{22}$ ,  $CO_2R^{22}$ ,  $CON(R^{20})_2$ ,  $SO_2R^{22}$  and  $R^{23}$ ;

and in a functional group when two  $R^{20}$  groups are present, when  $R^{20}$  and  $R^{21}$  are present, or when  $R^{20}$  and  $R^{23}$  are present, said two  $R^{20}$  groups,  $R^{20}$  and  $R^{21}$  or said  $R^{20}$  and  $R^{23}$  may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

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Also included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

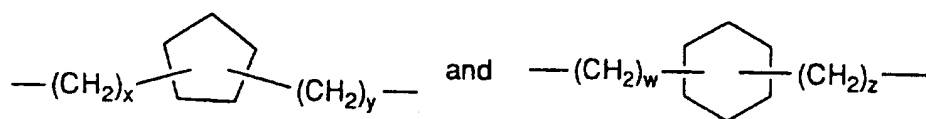
Also included in the invention is a method of treating a  
 5 cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective to treat said cytokine mediated disease.

### DETAILED DESCRIPTION OF THE INVENTION

10 The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred  
 15 straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion or by a carbonyl  
 20 group. Examples of cycloalkylene interruption include the following:



wherein: x and y = from 0-10 and w and z = from 0-9. Examples of  
 25 carbonyl interruption include - (CH<sub>2</sub>)<sub>x</sub>-C(O)-(CH<sub>2</sub>)<sub>y</sub> - .

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight,  
 30 branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.



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The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

10 The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

15 Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

25 The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type

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are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine and pyrazine and triazine.

The group  $\text{Ar}^1$  represents a 5-10 membered aryl group. The preferred aryl group is selected from phenyl and naphthyl.

The group  $\text{Ar}^2$  represents a 5-10 membered aryl or heteroaryl group. Preferred are phenyl, naphthyl, pyridyl, pyrimidinyl, thiophenyl, furanyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl and isoxazolyl.

$\text{Ar}^1$  and  $\text{Ar}^2$  are substituted with 1 - 3 groups selected from  $\text{R}^a$ .

The group  $\text{HAr}$  represents a heteroaryl group which contains from 5 to 10 atoms. One to three atoms are heteroatoms which are selected from O, S and N. In addition, there may be up to two additional nitrogen atoms, and 0-1 additional O or S. The heteroaryl group may be unsubstituted or substituted with 1 - 3  $\text{R}^a$  groups.  $\text{HAr}$  is carbon linked except where it is a purinyl, imidazolyl or imidazopyridine in which case it may be attached via a nitrogen or carbon atom.

Preferred heteroaryl groups represented by  $\text{HAr}$  are as follows: pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridine and pyrimidinyl.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S, SO, SO<sub>2</sub> or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms. Heterocyclyl may also be interrupted by or contain one or two carbonyl groups.

The heterocyclyl is carbon or nitrogen linked, if said heterocyclyl is carbon linked and contains a nitrogen, then nitrogen may be substituted by R<sup>24</sup>. Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazo[4,5-  
5 c]pyridine, imidazoliny, piperazinyl, pyrrolidin-2-one, piperidin-2-one and the like.

The term "TNF mediated disease or disease state" refer to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such  
10 as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

The term "cytokine" as used herein is meant any secreted  
15 polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1  
20 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) and Tumor Necrosis Factor-beta (TNF- $\beta$ ).

By the term "cytokine interfering or cytokine suppressive amount" is mean an effective amount of a compound of formula I which will, cause a decrease in the *in vivo* levels of the cytokine to normal or  
25 sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically  
30 active forms. All of these compounds are contemplated to be within the scope of the present invention.

One subset of compounds of the invention includes compounds of formula I wherein Ar<sup>1</sup> represents phenyl or naphthyl, and Ar<sup>2</sup> is independently selected from:

- 10 -

- 5 a) phenyl,  
b) pyridyl,  
c) pyrimidinyl,  
d) thiophenyl,  
e) furanyl,  
f) imidazolyl,  
g) thiazolyl,  
h) isothiazolyl,  
i) oxazolyl,  
10 j) isoxazolyl and  
k) naphthyl.

Within this subset of compounds, all other variables are as previously defined with respect to formula I.

Another subset of compounds of the invention includes

- 15 compounds of formula I wherein  $\text{HAr}$  is selected from the group consisting of:

- a) pyridyl,  
b) quinolyl,  
c) purinyl,  
20 d) imidazolyl,  
e) imidazopyridine and  
f) pyrimidinyl.

Within this subset of compounds, all other variables are as originally defined with respect to formula I.

- 25 Another subset of compounds of formula I includes compounds wherein  $R^1$  represents hydrogen. Within this subset of compounds, all other variables are as originally defined with respect to formula I.

- 30 Another subset of compounds of formula I includes compounds wherein  $R^1$  represents  $C_{1-15}$  alkyl, unsubstituted or substituted, as originally defined. Within this subset of compounds, all other variables are as originally defined with respect to formula I.

Another subset of compounds of formula I includes compounds wherein  $R^2$  represents a member selected from the group consisting of:

- 5 a) CN;
- b)  $C(O)C_{1-6}$  alkyl;
- c)  $C(O)C_{1-6}$  alkylphenyl;
- d)  $CO_2H$ ;
- e)  $CO_2C_{1-6}$  alkyl
- 10 f)  $CO_2C_{1-6}$  alkylphenyl;
- g)  $CONH_2$ ;
- h)  $CONHC_{1-6}$  alkyl;
- i)  $C(O)N(C_{1-6} \text{ alkyl})_2$ ;
- j)  $SO_2NH_2$ ;
- 15 k)  $SO_2NHC_{1-6}$  alkyl and
- l)  $SO_2N(C_{1-6} \text{ alkyl})_2$ .

Within this subset of compounds, all other variables are as originally defined with respect to formula I.

Preferred compounds of formula I are realized when:

20  $Ar^1$  represents phenyl or naphthyl and  $Ar^2$  is independently selected from the group consisting of:

- a) phenyl,
- b) pyridyl,
- c) pyrimidinyl,
- d) thiophenyl,
- 25 e) furanyl,
- f) imidazolyl,
- g) thiazolyl,
- h) isothiazolyl,
- i) oxazolyl,
- 30 j) isoxazolyl and
- k) naphthyl;

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one, two or three  $R^a$  groups are present, and each  $R^a$  is independently selected from the group consisting of: halo,  $R^{21}$ ,  $OR^{23}$ ,  $NR^{20}R^{23}$ ,  $CO_2R^{23}$ ,  $CONR^{20}R^{23}$ ,  $SO_2R^{21}$  and  $S(O)R^{21}$ ;

5 HAr is selected from the group consisting of:

- a) pyridyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- 10 e) imidazopyridine and
- f) pyrimidinyl;

$R^1$  is:

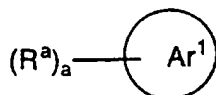
- a) H or
- 15 b) substituted or unsubstituted  $C_{1-15}$  alkyl; and

$R^2$  is selected from the group consisting of:

- a) CN;
- b)  $C(O)C_{1-6}$  alkyl;
- 20 c)  $C(O)C_{1-6}$  alkylphenyl;
- d)  $CO_2H$ ;
- e)  $CO_2C_{1-6}$  alkyl;
- f)  $CO_2C_{1-6}$  alkylphenyl;
- g)  $CONH_2$ ;
- 25 h)  $CONHC_{1-6}$  alkyl;
- i)  $C(O)N(C_{1-6} \text{ alkyl})_2$ ;
- j)  $SO_2NH_2$ ;
- k)  $SO_2NHC_{1-6}$  alkyl and
- 30 l)  $SO_2N(C_{1-6} \text{ alkyl})_2$ .

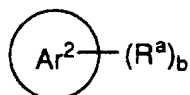
A more preferred subset of compounds of formula I is realized when:

- 13 -



is selected from the group consisting of:

- a) phenyl,
- b) 4-fluorophenyl,
- c) 4-chlorophenyl,
- d) 3-fluorophenyl,
- e) 3-chlorophenyl,
- f) 3-methyl phenyl,
- g) 3,4 dichlorophenyl and
- h) 3-hydroxyphenyl;



is selected from the group consisting of:

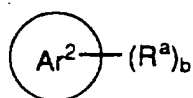
- a) 4-methylthiophenyl,
- b) 4-ethylthiophenyl,
- c) 3-methylthiophenyl,
- d) 2-methylthiophenyl,
- e) 3-ethylthiophenyl,
- f) 4-methylsulfonylphenyl,
- g) 4-ethylsulfonylphenyl,
- h) 3-methylsulfonylphenyl,
- i) 2-methylsulfonylphenyl,
- j) 4-methylsulfinylphenyl,
- k) 4-ethylsulfonylphenyl,
- l) 3-methylsulfinylphenyl,
- m) 4-(N-methyl-N-benzyl)aminomethylphenyl,
- n) 3-(N-methyl-N-benzyl)aminomethylphenyl,
- o) 4-methoxyphenyl,
- p) 4-hydroxyphenyl,
- q) 3-methoxyphenyl,
- r) 2-benzyloxyphenyl,
- s) 4-methylthiophen-2-yl,

- 14 -

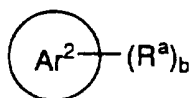
- t) 4-methylthiophen-3-yl,  
 u) 4-acetylamino-phenyl, and  
 v) 2-pyrimidinyl;

with the proviso that when  $(R^a)_a - \text{Ar}^1$  represents a)

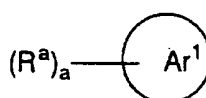
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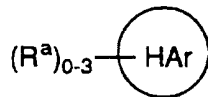
represents one of a) through u); and when



represents v),



10 represents one of b) through h);



is selected from the group consisting of:

- a) 4-pyridyl,  
 b) 4-(2-methylpyridyl),  
 c) 4-(2-aminopyridyl),  
 15 d) 4-(2-methoxypyridyl),  
 e) 4-quinolyl,  
 f) 4-pyrimidinyl,  
 g) 9-puriny,   
 h) 7-(imidazo[4,5-b]pyridinyl), and  
 20 i) 4-(3-methylpyridyl)

$R^1$  is H; and

$R^2$  is selected from the group consisting of:

25

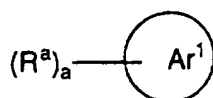
- a) CN;  
 b)  $C(O)C_{1-6}$  alkyl;  
 c)  $C(O)C_{1-6}$  alkylphenyl;



- 15 -

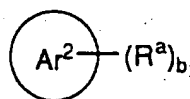
- 5
- d)  $\text{CO}_2\text{H}$ ;
  - e)  $\text{CO}_2\text{C}_{1-6}$  alkyl;
  - f)  $\text{CO}_2\text{C}_{1-6}$  alkylphenyl;
  - g)  $\text{CONH}_2$ ;
  - h)  $\text{CONHC}_{1-6}$  alkyl;
  - i)  $\text{C(O)N(C}_{1-6}\text{ alkyl)}_2$ ;
  - j)  $\text{SO}_2\text{NH}_2$ ;
  - k)  $\text{SO}_2\text{NHC}_{1-6}$  alkyl and
  - l)  $\text{SO}_2\text{N(C}_{1-6}\text{ alkyl)}_2$ .
- 10

Another more preferred subset of compounds of formula I is realized when:



is selected from the group consisting of

- 15
- a) phenyl,
  - b) 4-fluorophenyl,
  - c) 4-chlorophenyl,
  - d) 3-fluorophenyl,
  - e) 3-chlorophenyl,
  - f) 3-methyl phenyl,
  - g) 3,4 dichlorophenyl and
  - h) 3-hydroxyphenyl;
- 20



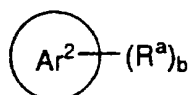
is selected from the group consisting of:

- 25
- a) 4-methylthiophenyl,
  - b) 4-ethylthiophenyl,
  - c) 3-methylthiophenyl,
  - d) 2-methylthiophenyl,
  - e) 3-ethylthiophenyl,
  - f) 4-methylsulfonylphenyl,
  - g) 4-ethylsulfonylphenyl,
  - h) 3-methylsulfonylphenyl,
- 30

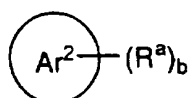
- 16 -

- i) 2-methylsulfonylphenyl,  
 j) 4-methylsulfinylphenyl,  
 k) 4-ethylsulfonylphenyl,  
 l) 3-methylsulfinylphenyl,  
 5 — m) 4-(N-methyl-N-benzyl)aminomethylphenyl,  
 n) 3-(N-methyl-N-benzyl)aminomethylphenyl,  
 o) 4-methoxyphenyl,  
 p) 4-hydroxyphenyl,  
 q) 3-methoxyphenyl,  
 10 r) 2-benzyloxyphenyl,  
 s) 4-methylthiophen-2-yl,  
 t) 4-methylthiophen-3-yl,  
 u) 4-acetylaminophenyl and  
 v) 2-pyrimidinyl;

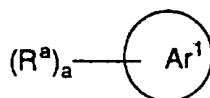
15 with the proviso that when  $(R^a)_a - \text{Ar}^1$  represents a)



represents one of a) through u), and when



represents v),



represents b) through h);

20  $(R^a)_{0-3} - \text{HAr}$  is selected from the group consisting of:

- a) 4-pyridyl,  
 b) 4-(2-methylpyridyl),  
 c) 4-(2-aminopyridyl),  
 d) 4-(2-methoxypyridyl),  
 25 e) 4-quinolyl,  
 f) 4-pyrimidinyl,  
 g) 9-purinyl,

- 17 -

- h) 7-(imidazo[4,5-b]pyridinyl) and
- i) 4-(3-methylpyridyl);

R<sup>1</sup> is substituted or unsubstituted C<sub>1-15</sub> alkyl; and

5

R<sup>2</sup> is selected from the group consisting of:

- a) CN;
- b) C(O)C<sub>1-6</sub> alkyl;
- c) C(O)C<sub>1-6</sub> alkylphenyl;
- 10 d) CO<sub>2</sub>H;
- e) CO<sub>2</sub>C<sub>1-6</sub> alkyl;
- f) CO<sub>2</sub>C<sub>1-6</sub> alkylphenyl;
- g) CONH<sub>2</sub>;
- h) CONHC<sub>1-6</sub> alkyl;
- 15 i) C(O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>;
- j) SO<sub>2</sub>NH<sub>2</sub>;
- k) SO<sub>2</sub>NHC<sub>1-6</sub> alkyl and
- l) SO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>.

20

Pharmaceutically acceptable salts of the compounds of formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of formula I formed e.g. from inorganic or organic acids. Conventional salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from 25 organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic and the like.

30

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming

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inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

Many of the compounds of the present invention have asymmetric centers. Consequently, the compounds occur as racemates, racemic mixtures and as individual diastereomers. All possible isomers, including optical isomers, are included in the present invention.

This invention also relates to a method of inhibiting the production or activity of cytokines in a mammalian patient in need of such treatment, which comprises administering to said mammal an amount of a compound of formula I which is effective for inhibiting the production or activity of cytokines, such that the cytokines are regulated to substantially normal levels, or in some cases to subnormal levels, so as to treat or prevent manifestations of the disease.

More particularly, the compounds of formula I can be administered to the mammalian patient in the treatment of the manifestations of disease states in which the symptoms or pathology are exacerbated or caused by excessive or unregulated production, levels or activity of IL-1, IL-6, IL-8 or TNF.

Compounds of formula I inhibit proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF, and are therefore useful for treating inflammation associated with diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

The compounds of formula I are administered to the patient in a general dosage range from as low as about 0.01 mg to as high as about 1.0 g, from about one to four times daily. Such dosages can be administered by conventional routes, e.g., orally, parenterally, topically, transdermally and the like. Obviously, the dosage employed will depend upon factors such as the route of administration, the potency of the particular compound administered, the severity of the patient's disease or condition, the incidence or severity of side effects and other factors.

More particularly, the compounds of formula I are useful to treat disease states and conditions in which excessive or unregulated TNF levels, production or activity is implicated, such as sepsis, including gram

negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host rejection, allograft rejections, fever and myalgia due to infection such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, AIDS and other viral infections, such as cytomegalovirus (CMV), influenza virus and the herpes family of viruses, such as Herpes Zoster or Simplex I and II.

As noted above, the compounds of formula I are administered to the patient in a general dosage range from as low as about 0.01 mg to as high as about 1.0 g, from about one to four times daily. With respect to diseases and conditions in which TNF is implicated, it is likely that the severity of these conditions will necessitate the use of higher doses than those employed for the treatment of less serious conditions such as inflammation.

The compounds of formula I can also be used topically in the treatment of inflammation, such as for the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; inflamed joints, eczema, psoriasis or other skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The compounds of formula I are also useful in treating diseases characterized by excessive IL-8 levels or activity. There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The invention includes a method of treating psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis

- 20 -

and glomerulonephritis, in a mammal in need of such treatment which comprises administering to said mammal a compound of formula I in an amount which is effective for treating said disease or condition.

Pharmaceutical compositions containing a compound of  
5 formula I are formulated in accordance with standard pharmaceutical practice. This invention encompasses a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The compounds of formula I may also be included in  
10 combination with a second therapeutically active ingredient.

The particular dosage form may be described, for example, as a solid, semi-solid, liquid or a vapor, as well as through its intended use as an oral, parenteral, transdermal, respiratory, topical, intravaginal, rectal, transmucosal or the like. All such compositions are included in  
15 the present invention.

Examples of solid oral dosage forms included herein are tablets, capsules, troches, lozenges and the like. Pharmaceutical carriers used in such dosage forms include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like.

20 Examples of liquid oral dosage forms included herein are syrups, solutions, suspensions, aerosols and emulsions. Exemplary of pharmaceutical carriers included in liquid oral dosage forms are water, peanut oil, olive oil, water, ethanol and the like. Additionally, solid ingredients can be included in the liquid dosage forms, which are soluble,  
25 swellable or suspendable.

Parenteral dosage forms include intravenous and intramuscular injections, intravenous and intramuscular preparations in freeze-dried or other solid form for dissolution or reconstitution and implantable tablets. The carrier includes the liquids used in the  
30 preparation, as well as any non-therapeutically active components that are included.

Similarly, the carrier or diluent may include time delay material well known in the art, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

When a liquid is used, the preparation is in the form of a syrup, emulsion, soft gelatin capsule, sterile liquid or nonaqueous liquid suspension.

The compounds of formula I may be administered topically.

- 5 Topical liquids include solutions, suspensions and emulsions. Topical solids include powders, poultices and the like. Topical semi-solids include creams, ointments, gels and the like.

- 10 The amount of a compound of formula I, for all methods of use disclosed herein, required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the condition, whether and the discretion of the physician. An example of a topical dose of a compound of formula I is as low as from about 0.01 mg to as high as about 2.0 g, administered one to four, preferably one to two times daily.

- 15 The active ingredient may comprise from as low as about 0.001% to as high as about 90% w/w of the composition.

- 20 Drops according to the present invention may comprise sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be  
25 sterilized by filtration and transferred to the container by aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol,  
30 diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may

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be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

5 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an  
10 aqueous or non-aqueous liquid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic  
15 acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and  
20 other ingredients such as lanolin may also be included.

The methods of the instant invention may be carried out by administering the compound of formula I to a patient in need of such treatment. The term 'parenteral' as used herein includes intravenous, intramuscular, or intraperitoneal administration. The subcutaneous and  
25 intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The instant invention can also be carried out by delivering the monokine activity interfering agent subcutaneous intranasally, intrarectally, transdermally, or intravaginally

30 The compounds of formula I may also be administered by inhalation. By 'inhalation' is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by convention techniques.

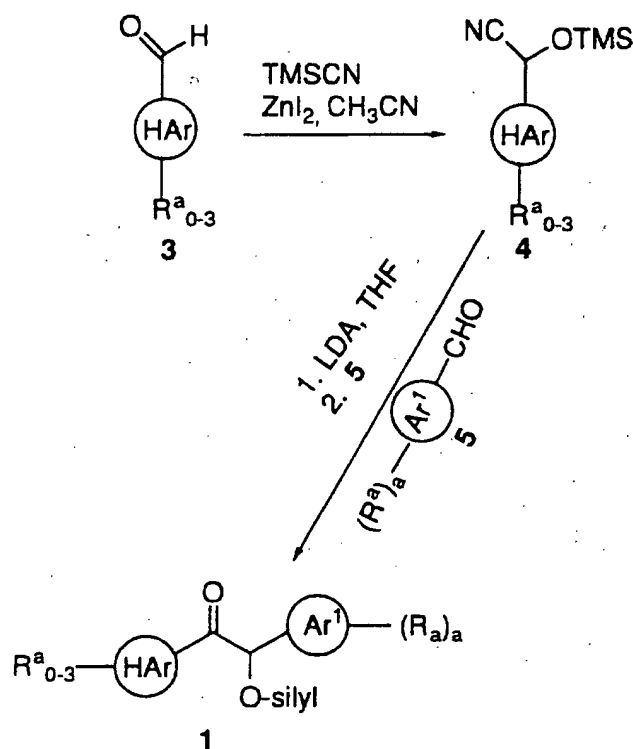


Compounds of formula I are pyrrole derivatives which may be prepared according to the procedures set forth below. The key process in preparing compounds of formula I is the formation of a pyrrole ring with specific substituents on the heterocycle.

5. Compounds of formula I are prepared (see Scheme I) by the reaction of compound 1, or a protected version thereof, with an acetophenone in the presence of potassium cyanide followed by treatment with an alkyl or aryl amine, ammonia or equivalent thereof (ammonium acetate) at elevated temperature.

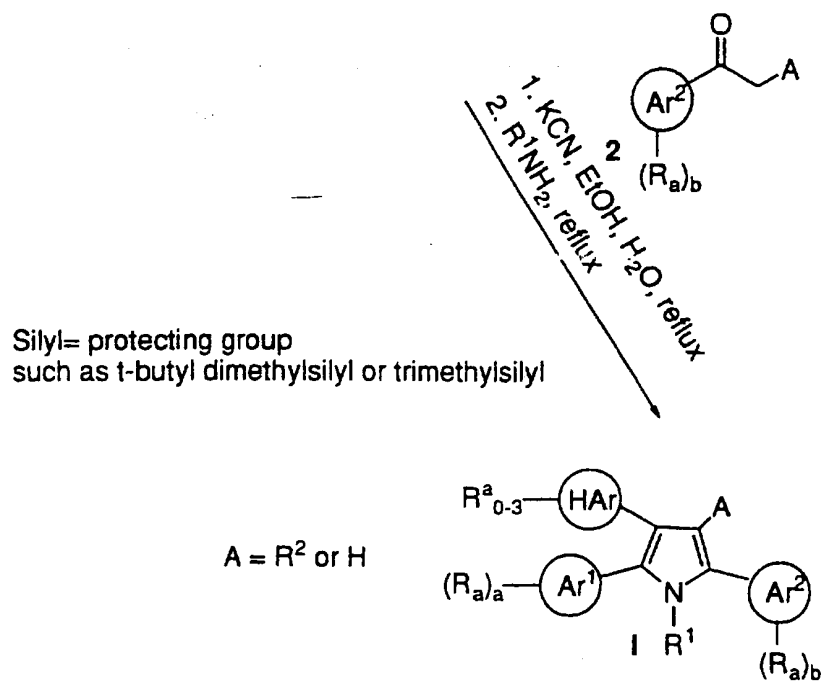
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SCHEME I



TMSCN = trimethylsilyl cyanate  
 LDA = lithium diethylamide  
 TMS = trimethylsilyl

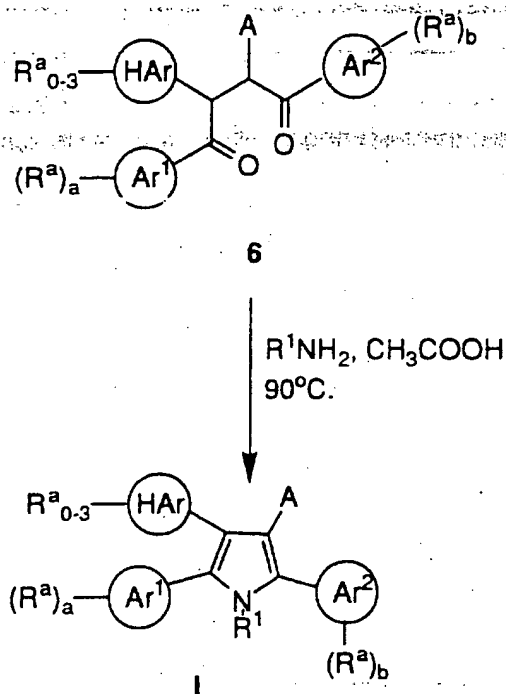
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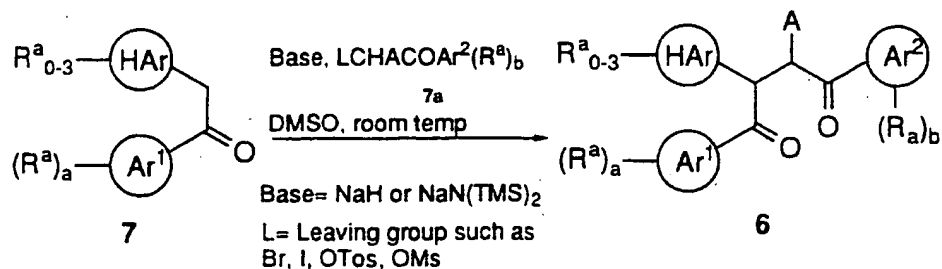
Heteroaromatic aldehydes 3 may be converted to their trimethylsilyl cyanohydrins 4. Deprotonation and reaction with an aldehyde 5 will provide trimethyl silyl protected benzoin 1. (See, e.g., Hunig, S. et al., *Chem. Ber.* 112, 2062 (1979)).

- 25 -

## SCHEME II

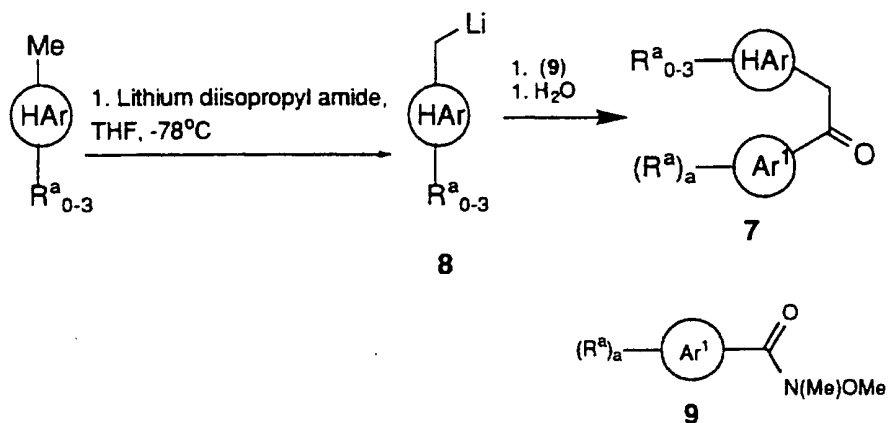


- Condensation of the 1,4-diketone 6 with ammonia gives rise to pyrroles (Paal Knor Synthesis). Compound 6, a 1,4 diketone, (see Scheme II) is reacted with ammonia, or a compound that gives rise to ammonia, such as ammonium acetate or a primary amine, to provide compounds of formula I. This reaction can be conducted in the presence of an acid catalyst, such as acetic acid or titanium tetrachloride at an elevated temperature. 1,4 diketones 6 are thus regioselectively constructed so that the appropriate groups are present on the pyrrole ring.



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Alkylation of 1-aryl-2-heteroarylethanones **7** with bromoacetophenones or other leaving group substituted acetophenones **7a** provides 1,4 diketones **6** (Iyer, R. N., et al. Ind. J. Chem. **11**, 1260, (1973)). Bromoacetophenones are readily prepared by bromination of acetophenones (for example by treatment with bromine in acetic acid or benzyltrimethylammonium bromide).

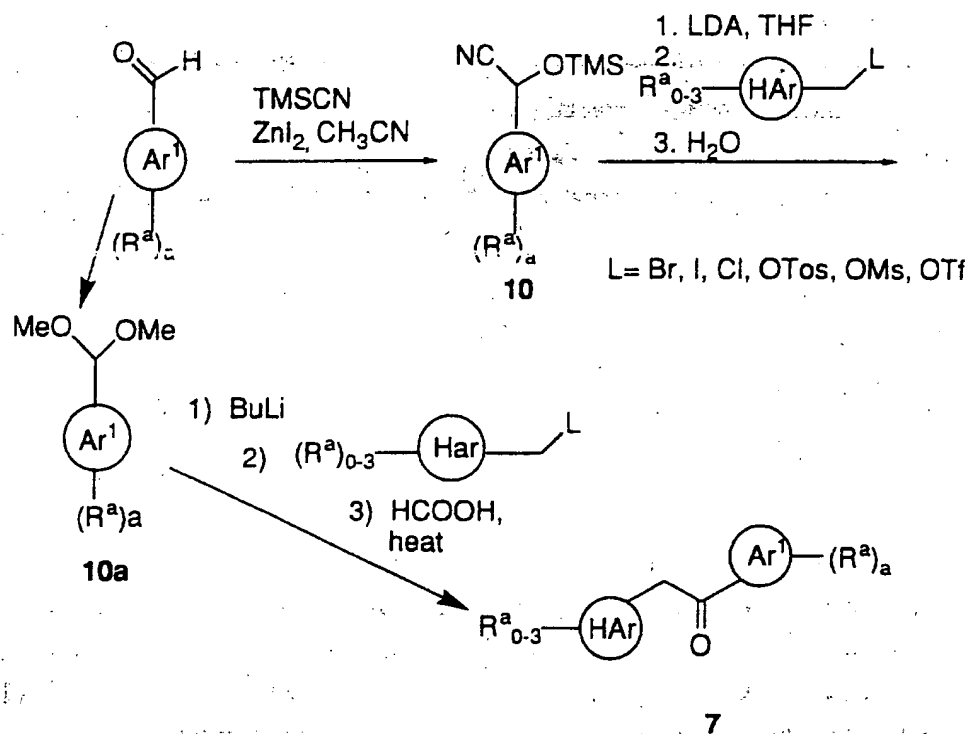


10

Ethanone **7** is prepared by the addition of a heteroaryl methyl anion **8** to an activated benzoic acid **9** (for example esters, acid chlorides, nitriles and N-methoxy-N-methyl amides) (See, e.g., Wolfe, J. F. et al. J. Org. Chem. **39**, 2006 (1974), Kaiser, E. M. et al. Synthesis **705** 1975 and Ohsawa A. Chem. Pharm. Bull. **26**, 3633, (1978)).

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7

An alternative approach to the synthesis of compound

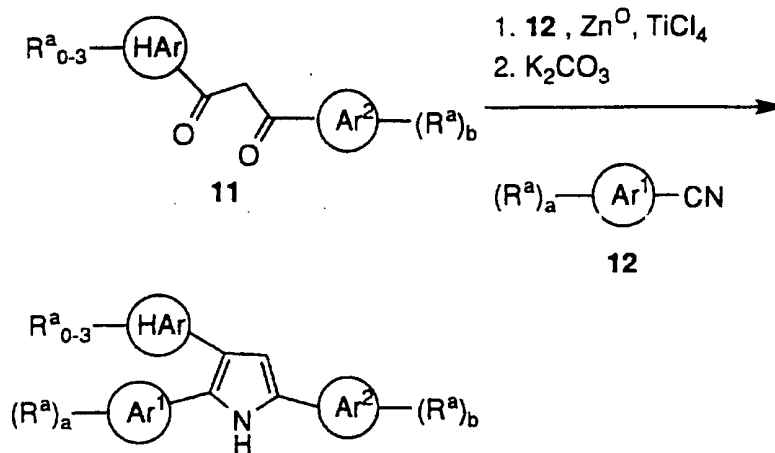
7 is via an alkylation of aryl trimethyl silyl protected cyanohydrin 10.

- 5 Treatment of 10 with lithium diisopropyl amide in THF and addition of a heteroaryl methyl group functionalized with a leaving group L (e.g., Br, I, Cl, tosylate, mesylate) followed by acid catalyzed hydrolysis of the silyl cyanohydrin group will provide ethanones such as 7 (Deuchert, K., et al. Chem. Ber. 112, 2045, 1979).

- 10 Dimethyl acetals 10a may be prepared from aldehydes by treatment with trimethylorthoformate and an acid catalyst. Addition of a base such as butyl lithium followed by an alkylating agent will, after hydrolysis of the acetal, provide 7.

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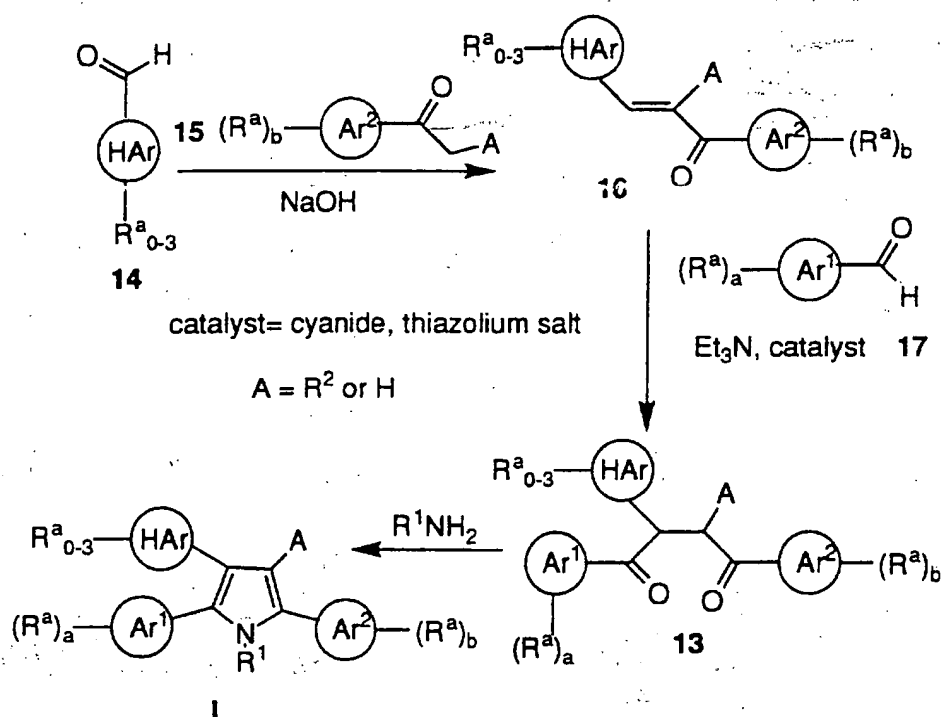
SCHEME III



5 The reductive cross coupling of 1,3 diketones **11** with a nitrile **12** in the presence of zinc and titanium tetrachloride also gives rise to compounds where the pyrrole is unsubstituted at position 4. See Scheme III, (Gao, J. et al. Tet Lett. 34, 1617, 1993). 1,3 diketones **11** may be prepared by alkylation of **4** with bromoacetophenones.

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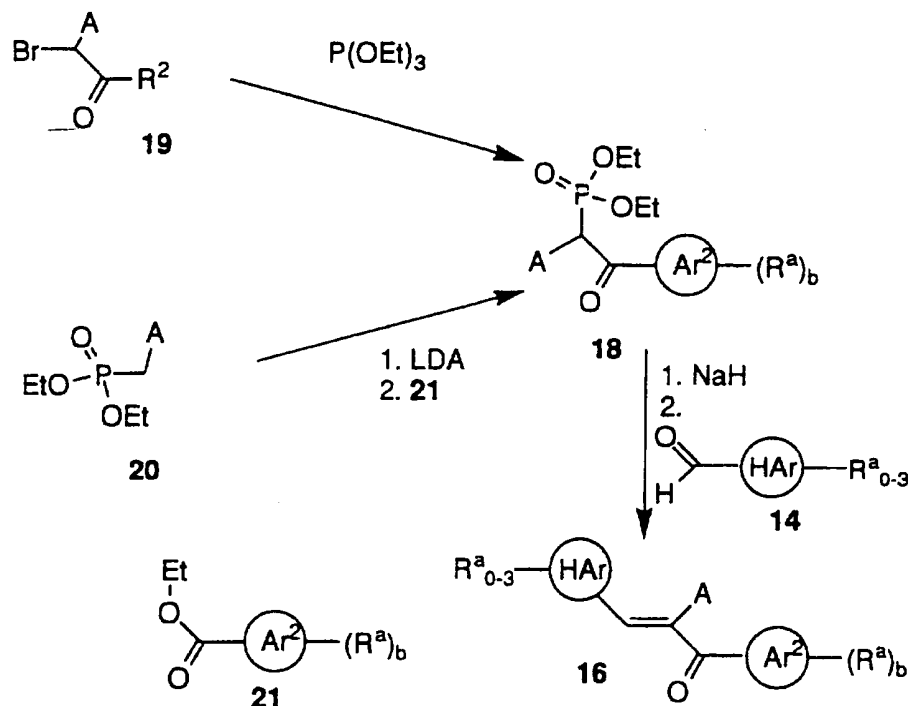
SCHEME IV



1,4 diketones 13 are also prepared as described in Scheme IV. A heteroaryl aldehyde 14 is condensed with a methyl ketone 15 to provide  $\alpha,\beta$ -unsaturated ketone 16. In the presence of a catalyst such as cyanide or a thiazolium salt an aryl aldehyde 17 reacts with 16 to give 13 (Stetter, H. J. et al Heterocyclic Chem. 14, 573, (1977) and Stetter, H. et. al. Organic Reactions, Vol 40, 407-496). Condensation of 13 with an amine provides compounds of formula I.

- 30 -

SCHEME V

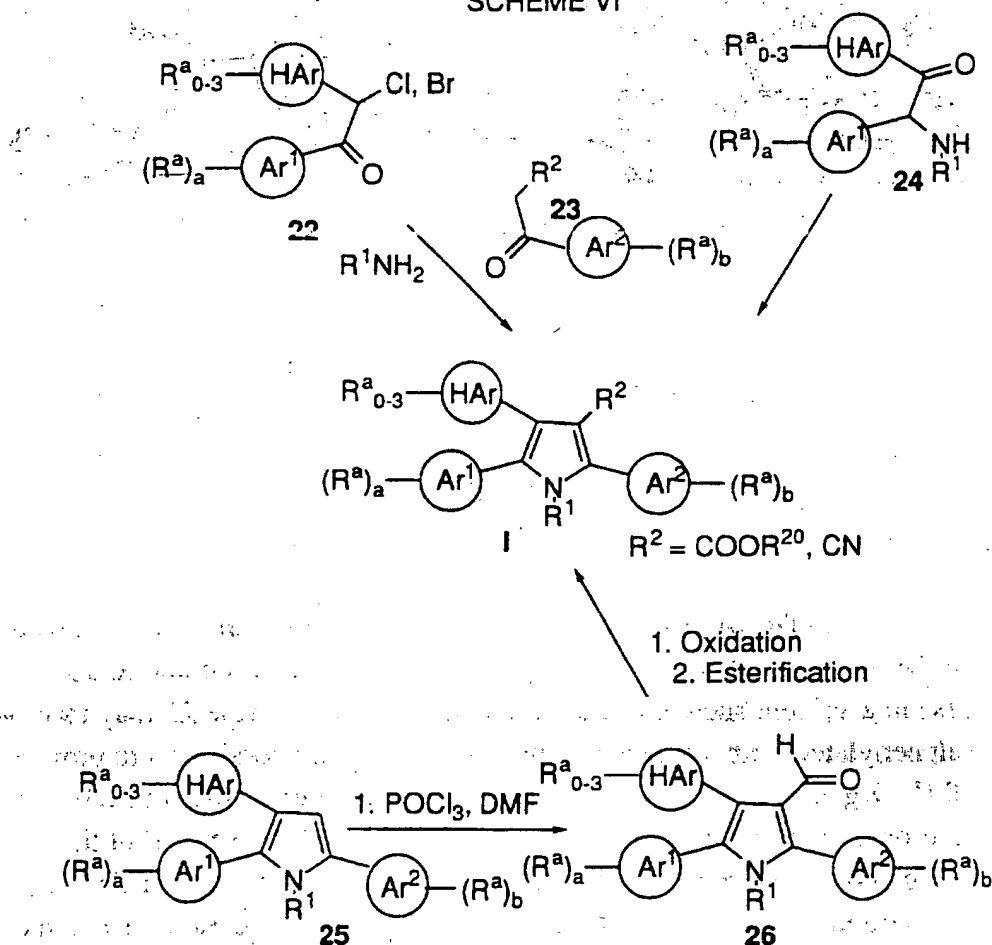


- Intermediate **16** may be prepared by a Horner-Emmons reaction of the anion of **18** with the heteroaryl aldehyde **14**. The reagent
- 5 **18** may be prepared by reaction of the bromoketone **19** and triethyl phosphite or by reaction of the lithium salt of diethyl methylphosphonate with an ester **21**.



- 31 -

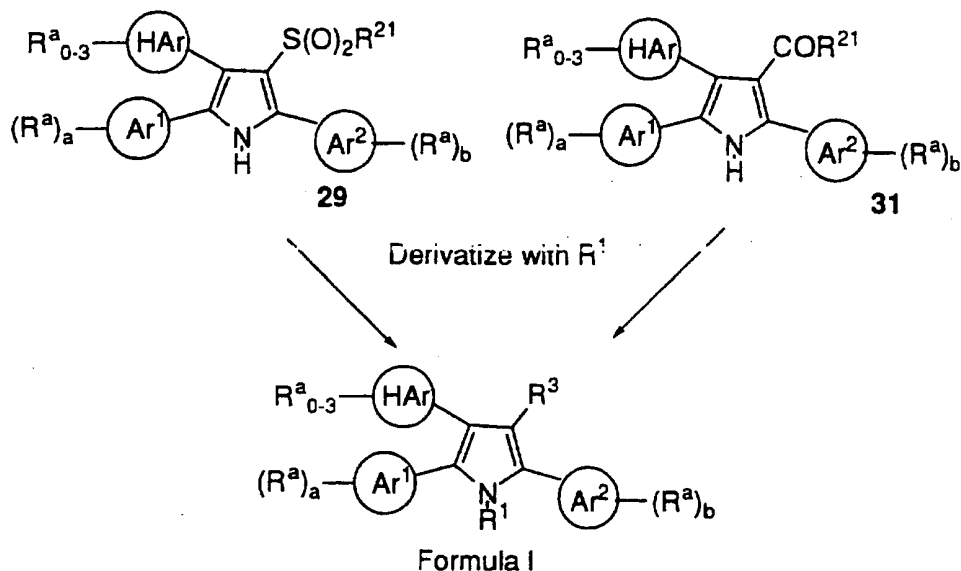
SCHEME VI



The ester and nitrile of formula I may be prepared as shown in Scheme VI by treatment of halo ketones 22 with keto esters or keto nitriles 23 with ammonia or an amine producing ester I (Hantzsch. Ber. Dtsch. Chem. Ges. 23, 1474, 1890). Alternatively a 2-amino ketone 24 reacts with a 3-keto ester 23 to produce I.

A further method of synthesis of Compounds of formula I is by oxidation and esterification of aldehyde 26. The aldehyde is prepared by treatment of the pyrrole 25 with the Vilsmeier reagent ( $\text{POCl}_3/\text{DMF}$ ).

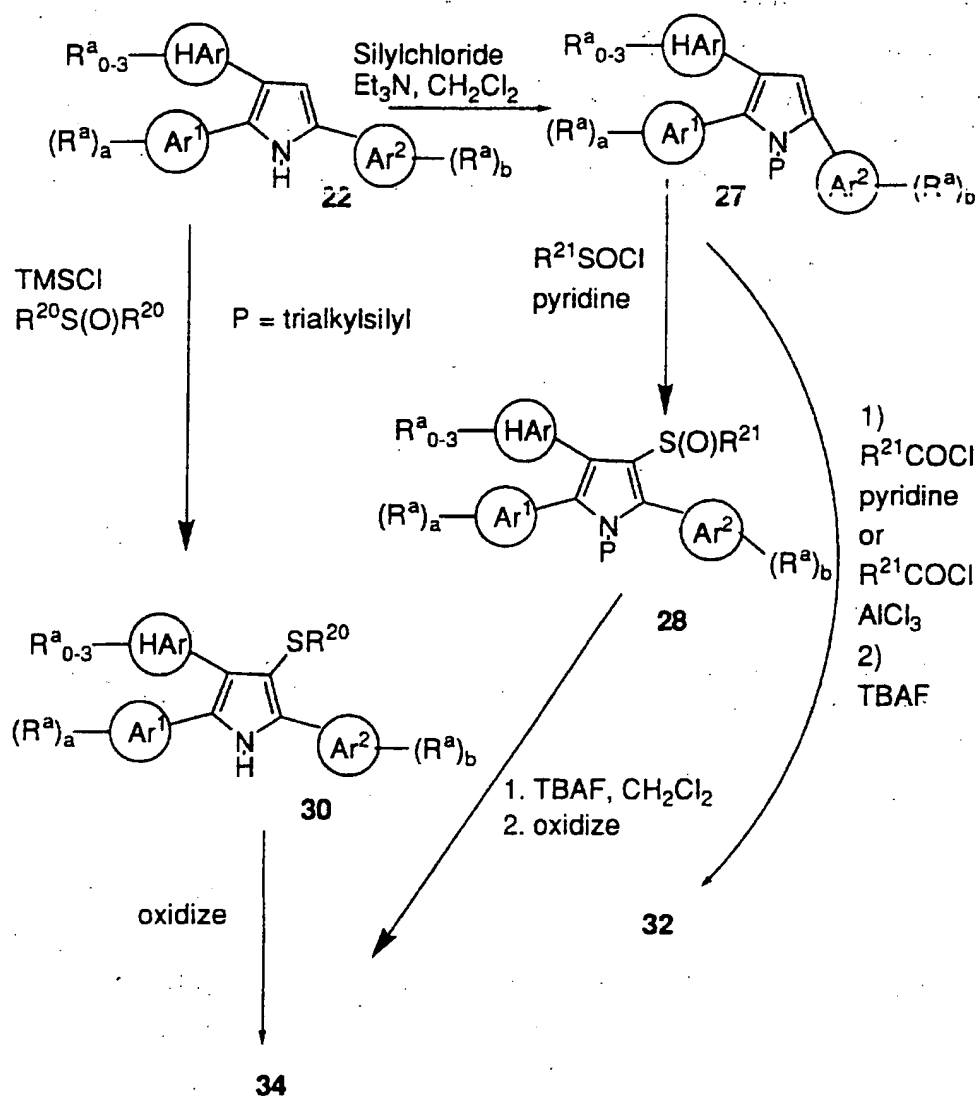
- 32 -



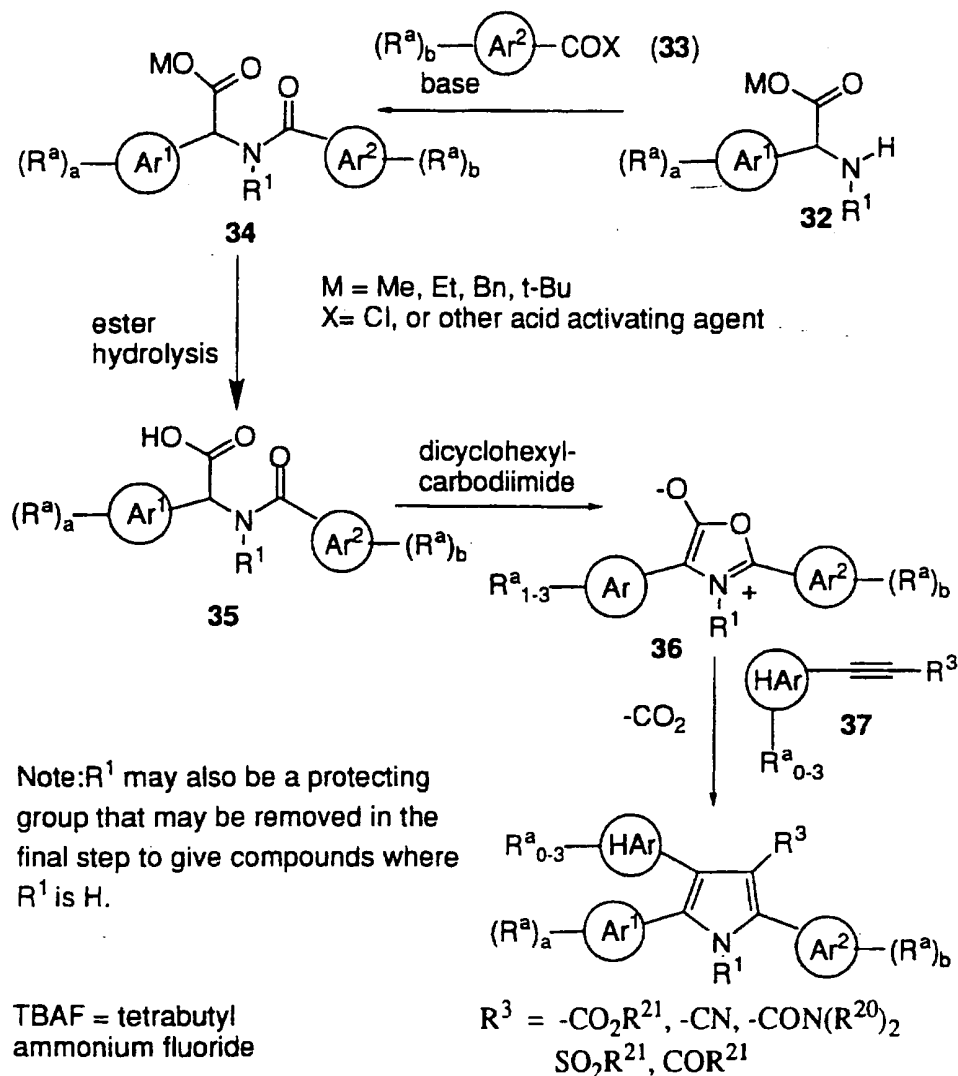
- The pyrrole 22 prepared as described herein may be silylated on the nitrogen atom to give 27 by treatment with a silyl chloride and base in a solvent such as methylene chloride. The pyrrole 27 may then be sulphenylated with a sulphenylchloride under basic conditions to provide 28 (J. Org. Chem. 6317 1990). Oxidation of 28 with a reagent such as m-chloroperoxybenzoic acid will give the sulphone 29. Removal of the silyl group and derivatization of the pyrrole will give compounds of Formula I. Compound 22 may also be converted to the sulphide 30 by reaction of 22 with a symmetrical sulfoxide in the presence of trimethylsilylchloride (TMSCl) to give 30. Oxidation of 30 with a reagent such as m-chloroperoxybenzoic acid will give 29. The silyl pyrrole 27 may also be acylated with an acid chloride to give the ketone 31.
- Removal of the silyl group from 31 and derivatization of the pyrrole will give compounds of formula I. Pyrroles such as 22 may also be sulfinylated directly without N-protection, by treatment with sulphinyl chloride in a solvent such as dichloromethane at 0°C (J. Org. Chem. 5336, 1980). Oxidation as described above thus provides pyrroles of formula I where  $R^3$  is  $SO_2R^{21}$ .

- 33 -

## SCHEME VII



- 34 -

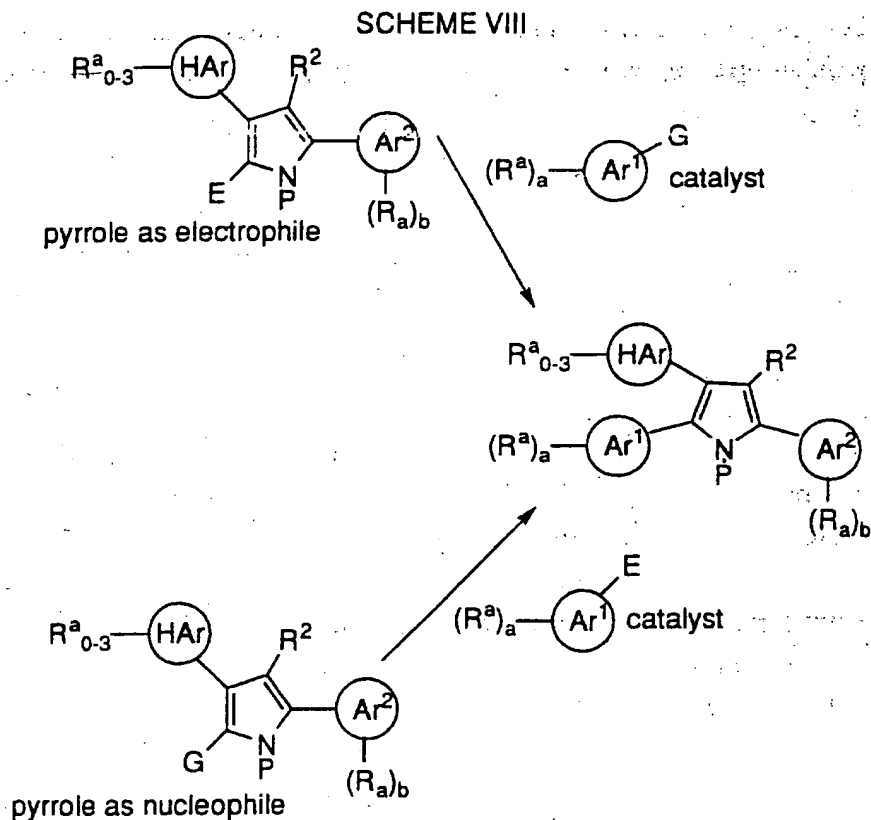


- 5 The amino acid ester 32 may be acylated with an acid 33 that is suitably activated (acid chloride or other activating group used in amide coupling reactions) to give 34. Hydrolysis of the ester protecting group will provide 35. Cyclization by treatment with an acid activating group such as dicyclohexylcarbodiimide (DCC) will give the oxazolium species 36. Addition of an alkyne 37 to 36 may give a pyrrole of

- 35 -

Formula I via a 3+2 cycloaddition followed by loss of carbon dioxide.

Various  $R^3$  groups may be incorporated in this manner.



E=: Br, I, OSO<sub>2</sub>CF<sub>3</sub>

G=: SnMe<sub>3</sub>, B(OH)<sub>2</sub>, ZnCl, MgBr

catalyst=: Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>

P=R<sup>1</sup> or protecting group such as trialkyl silyl, benzyl, substituted benzyl, t-butyloxycarbonyl

5

Aryl and heteroaryl rings may also be appended to the pyrrole ring system by utilization of organometallic coupling technology (Kalinin, V. Synthesis 413 1991). The pyrrole ring may function as an electrophile or as a nucleophile.

- 36 -

Any of the three appended aromatic or heteroaromatic rings may be attached to the pyrrole ring system (Alvarez, A. J. et al J. Org. Chem. 1653, 1992 (use of boronic acid and tributyl stannanes for coupling to aromatic and heteroaromatic rings)). Attachment of pyrrole pendant groups may be carried out with or without other Ar, HAr, R<sup>2</sup> or R<sup>3</sup> groups attached.

The synthesis of pyrroles containing nucleophilic groups for coupling reactions depends on the pyrrole substitution pattern. Lithium anions are prepared by metalation of a regioselectively halogenated pyrrole, or the regioselective deprotonation of the pyrrole preferably by the use of a directing functional group. The resulting anion may then be trapped by a trialkyl stannyl halide or a trialkyl borate or transmetalated to magnesium or zinc by treatment with appropriate halide salts. A further method used to incorporate a trialkyl stannyl group is the coupling of a bromo, iodo or triflate substituted pyrrole with hexalkylditin in the presence of a palladium catalyst.

The synthesis of pyrroles incorporating electrophilic groups may be carried out by the regioselective halogenation of a pyrrole (Pyrroles Part I, R. Alan Jones, ed., Heterocyclic Compounds Vol 48 Part 1, John Wiley, New York, 349-391, 1990). The regioselectivity of halogenation will depend on the size, nature and substitution position on the pyrrole ring as well as the presence or absence of the N-alkyl protecting group. Triflates may be prepared by acylation of hydroxy pyrroles with triflic anhydride.

The reaction conditions used will depend on the nature of the coupling species. In the case of magnesium, zinc and stannyl coupling reactions the solvent employed is toluene, or DMF under anhydrous conditions. In the case of boronic acid couplings a heterogeneous system is used of water, toluene, and dimethoxyethane, or ethanol in the presence of a base such as sodium carbonate, or bicarbonate. In general, the reaction takes place at an elevated temperature (80-100 °C.). The catalysts used will most likely depend on the structure of the components to be coupled as well as the functional groups and belong to the group

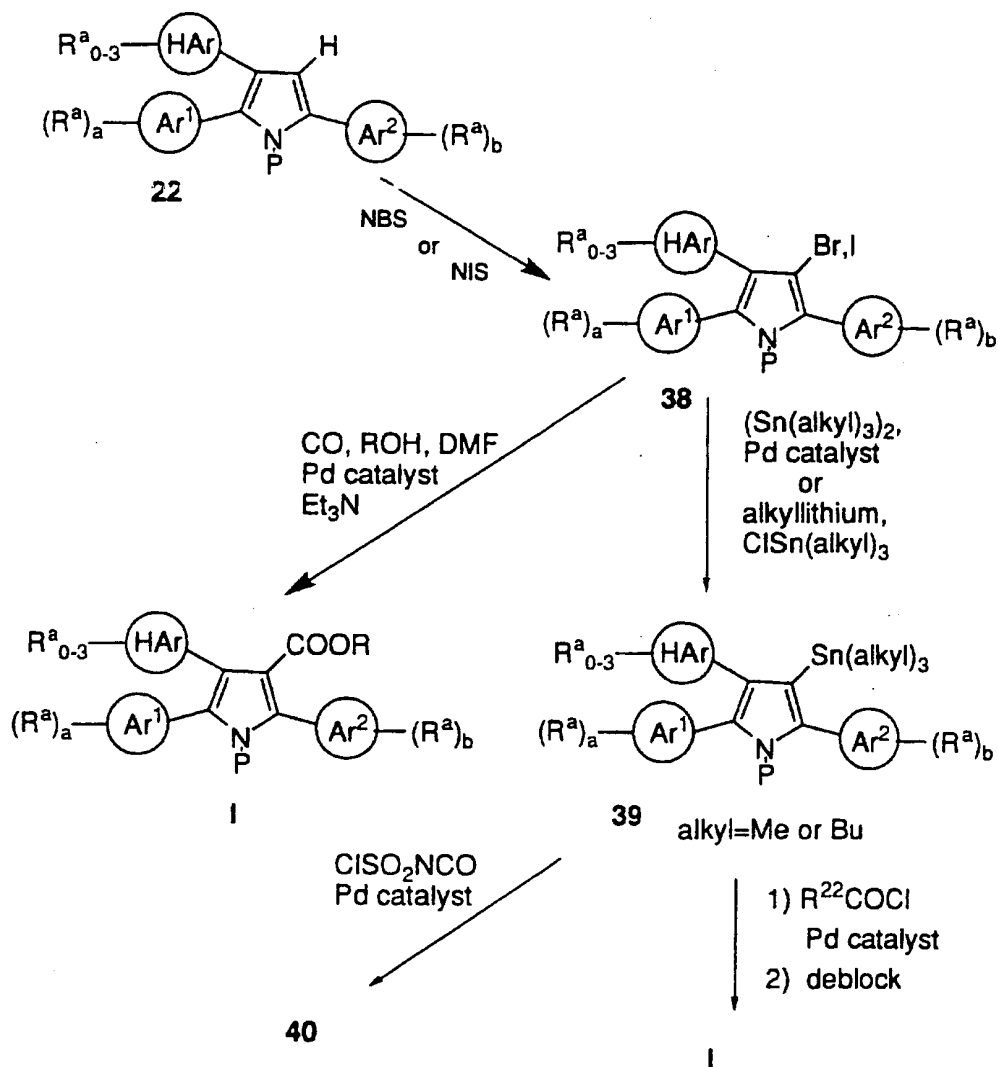
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consisting of tetrakis(triphenylphosphine)palladium (0), or palladium bis triphenyl phosphine dichloride.

Coupling chemistry may be utilized to introduce R<sup>3</sup> groups as shown below in Scheme X. 4-unsubstituted pyrroles optionally  
5 protected at nitrogen (P) 22 may be halogenated by treatment with electrophilic sources of bromine and iodine to provide 38. The halogen may then be coupled with carbon monoxide in the presence of an alcohol to give, after removal of the protecting group, 4-alkoxycarbonyl substituted pyrroles of formula I. Treatment of 38 with a hexalkylditin  
10 in the presence of a palladium catalyst (see above for examples of catalysts) will give the stannyl pyrrole 39. Alternatively, halogen metal exchange through treatment of 38 with an alkyl lithium followed by addition of a trialkyltin chloride will give 39. The stannyl pyrrole may then be coupled to acid chlorides to give ketones of formula I after  
15 deblocking, if required. Reaction of 39 with chlorosulfonylisocyanate in the presence of a palladium catalyst will give the sulphonyl isocyanate 40. 40 may subsequently be converted to a sulphonyl urea or sulphonyl carbamate of formula I by addition of a primary or secondary amine or an alcohol after deblocking (acid conditions for P = CO<sub>2</sub>-t-Bu; basic  
20 hydrolysis for P = SO<sub>2</sub>Ph), if required.

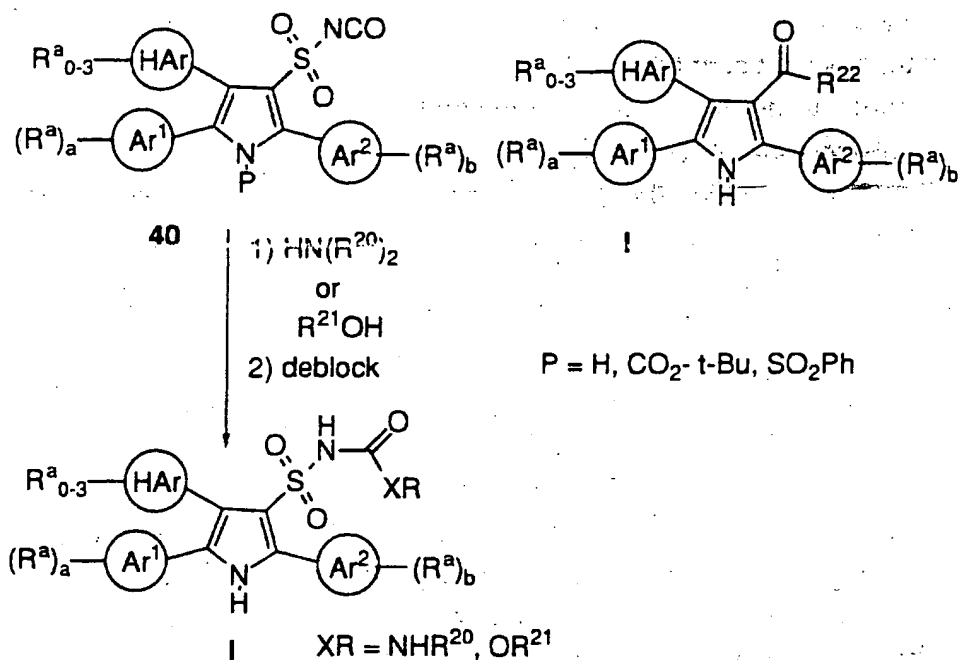
- 38 -

SCHEME IX





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Coupling of alkenes or alkynes with 4-halo pyrroles (Heck reaction, see Kalinin, V. Synthesis 413 1991 for a review) will give rise to R<sup>2</sup> (generic nomenclature) alkenyl and alkynyl substituted pyrroles that may be reduced or otherwise modified to provide compounds of formula I.

Functional groups such as halogens, sulfides, nitro groups, ethers and other groups stable to the reaction conditions used in the linear synthesis of the pyrroles are incorporated in the initial steps of the reaction sequence. Sulfides may be oxidized to sulfoxides and sulfones with reagents such as m-chloroperbenzoic acid. Sulfides may also be converted to sulfonyl chlorides by oxidation and chlorination by chlorine in water.

Primary amines are prepared from nitro groups by catalytic (Pd/C, H<sub>2</sub> or Raney Nickel, H<sub>2</sub>) or chemical means (CoCl<sub>2</sub>, NaBH<sub>4</sub>). Alkylation of amines to give secondary and tertiary amines is achieved by reductive alkylation (aldehyde, NaCNBH<sub>4</sub>) or alkylation with an alkyl group substituted with a leaving group in the presence of a base such as K<sub>2</sub>CO<sub>3</sub>. Tertiary amines may, alternatively, be carried through the

- 40 -

reaction sequences to the pyrroles. Acylation of primary or secondary amines with activated acids, chloroformates, isocyanates and chlorosulfonates will give rise to amides, carbamates, ureas and sulfonamides, respectively.

- 5           Other methods of preparing amides and ureas are useful: such as for example, treatment of the amine with phosgene, or an equivalent thereof, followed by acylation of an alcohol or amine with the intermediate activated chloroformamide.

- 10           Carboxylic acids are best introduced as esters early in the synthesis. Saponification will provide carboxylic acids. Transesterification or esterification of the acids will give esters. Carboxylic acids may be converted to amides by activation and reaction with amines. Phenols are best introduced in a protected form early in the synthetic sequence to the pyrrole. Removal of the protecting group provides a phenol which  
15           may subsequently be alkylated in the presence of an alkylating agent and base to give an ether, or acylated with an isocyanate to give carbamates. Phenols may be converted to aryl ethers by reaction with an aryl bismethane in the presence of copper II acetate.

- 20           Aryl and heteroaryl groups may be attached to pyrrole pendant aryl and heteroaryl groups by application of coupling chemistry technology as outlined above.

- The sequence and conditions of the reaction steps is dependent on the structure and functional groups present. Protecting groups may be necessary and may be chosen with reference to Greene, T.W., et al.,  
25           Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., 1991. The blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include  
30           chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with fluoride ion, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation.

          Examples of suitable hydroxyl protecting groups are:

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t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and allyloxycarbonyl. Examples of suitable carboxyl protecting groups

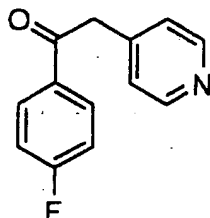
5 are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyl, dimethoxysilyl, t-butylidiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl and t-butyl.

10 The following examples are illustrative and are not limiting of the compounds of this invention.

#### PREPARATIVE EXAMPLE 1

##### 4-Fluoro-2-(4-pyridyl)acetophenone (1)

15



To a solution of lithium diisopropyl amide (Aldrich Chemical Co. 2.0 M in heptane, THF ethyl benzene) 3.1 mL (6.3 mmol)

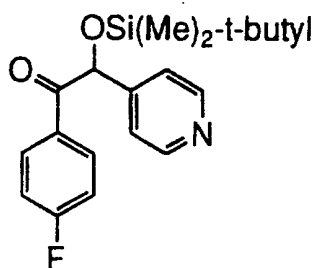
20 in 6 mL of anhydrous THF at -78°C under nitrogen was added 0.5 g (5.3 mmol) of 4-picoline dropwise. The reaction mixture was stirred for 20 minutes and then treated with a solution of 0.9 g (5.3 mmol) of 4-fluoro-(N-methyl-N-methoxy)-benzamide in THF. The reaction mixture was warmed to 0°C and quenched by addition of 10 mL of brine. The mixture

25 was extracted with ethyl acetate (EtOAc) (3 x 10 mL) and the combined organic phases were dried over MgSO<sub>4</sub>. The mixture was filtered and the filtrate was concentrated in vacuo to give the title compound as an orange solid.

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$^1\text{H}$  NMR ( $\text{CDCl}_3$  300 MHz): 4.23 s (d, 2H), 7.1-7.18 m (4H), 8.02 (dd, 2H), 8.55 (dd, 2H).

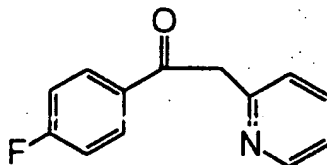
5

PREPARATIVE EXAMPLE 2

To a 2 liter 3 neck flask equipped with a mechanical stirrer  
under  $\text{N}_2$  was added 54.6 g (0.59 m) diisopropylethylamine and 150 ml  
of THF. The solution was cooled to  $-20^\circ\text{C}$  and treated with 268 ml (0.67  
m) of 2.5 M butyl lithium over 20 minutes. To the reaction mixture was  
added 125 g (0.56 m) of 4-(t-butyldimethylsilyloxymethyl)-pyridine in  
100 ml of THF over 30 minutes. The reaction mixture was stirred for  
1 hour at  $-15^\circ\text{C}$  and then treated with a solution of 108 g (0.59 m) of 4-  
fluoro-(N-methyl-N-methoxy)-benzamide dissolved in 100 ml of THF  
dropwise. The reaction was warmed to  $0^\circ\text{C}$  and stirred for 1 hour and  
then was warmed to room temperature and was quenched by addition of  
1 liter of 20%  $\text{NH}_4\text{Cl}$  solution. The aqueous phase was extracted with  
EtOAc (3 x 500 ml). The combined organic phases were washed with  
water (1 x 500 ml), 1 x 500 ml brine and were dried over  $\text{MgSO}_4$ . The  
mixture was filtered and the filtrate was concentrated in vacuo to give a  
dark oil. The product was purified by flash chromatography over silica  
gel eluting with 10-20% EtOAc/hexanes.

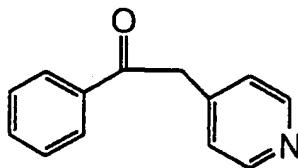
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PREPARATIVE EXAMPLE 34-Fluoro-2-(2-pyridyl)acetophenone (3)

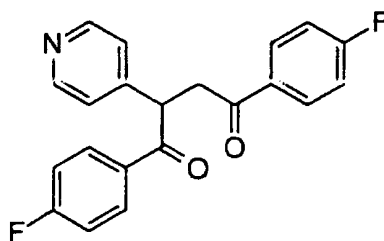
5 To a solution of lithium diisopropyl amide (Aldrich Chemical Co. 2.0M in heptane, THF ethyl benzene) 5.2 mL (10.5 mmol) in 6 mL of anhydrous THF at -78°C under nitrogen was added 0.93 g (10 mmol) of 2-picoline dropwise. The reaction mixture was stirred for 20  
10 minutes and then treated with a solution of 1.71 g (5.3 mmol) of 4-fluoro-(N-methyl-N-methoxy)-benzamide in THF. The reaction mixture was warmed to 0°C and quenched by addition of 10 mL of brine. The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were dried over MgSO<sub>4</sub>. The mixture was filtered and the filtrate  
15 was concentrated in vacuo to give a solid.

H<sup>1</sup> NMR (CDCl<sub>3</sub> 300 MHz): 4.49 (s); 6.0 (s); 6.97 (m); 7.3-7.12 (m); 7.62 (m); 7.82 (m); 8.10 (dd); 8.28 (bd); 8.57 (bd). Relative integrations are not meaningful as the compound exists in a keto/enol equilibrium as  
20 determined by H<sup>1</sup>-NMR. FAB ms: 216 (M<sup>++</sup>1).

PREPARATIVE EXAMPLE 42-(4-pyridyl)acetophenone (4)

25

As in Preparative Example 3 utilizing N-methyl-N-methoxy-benzamide as the acylating reagent compound 4 is prepared.

PREPARATIVE EXAMPLE 5

5 To a solution of 0.14 g (0.67 mmol) of 4-fluoro-2-(4-pyridyl)acetophenone (1) from Preparative Example 1 in 2 mL of anhydrous DMSO under nitrogen at room temperature was added 0.67 mL of a 1.0M solution of sodium hexamethyl disilazide in THF. After 15 minutes a solution of 4-fluoro-bromoacetophenone 0.14 g (0.67

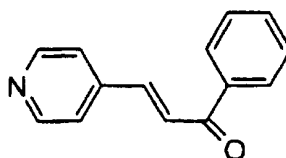
10 mmol) in DMSO was added dropwise. The reaction mixture was diluted with 5 mL of water after 30 minutes and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were washed with brine and dried over  $\text{MgSO}_4$ . The mixture was filtered and the filtrate was concentrated in vacuo to give an oil.

15

$^1\text{H}$  NMR ( $\text{CDCl}_3$  300 MHz): 3.26 (dd, 1H); 4.12 (dd, 1H); 5.23 (dd, 1H); 7.04-7.13 (m, 4H); 7.27 (dd, 2H); 7.95-8.05 (m, 4H); 8.51 (d, 2H).

PREPARATIVE EXAMPLE 6

20



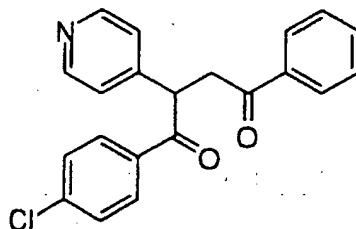
To 4.4 ml of dry pyridine under nitrogen was added 2.14 g (0.02 mol) of pyridine-4-carboxaldehyde followed by 2.4 g (0.02 mol)

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acetophenone and 1.46 g (0.02 mol) diethylamine. The solution was refluxed for 2.5 hours, cooled to room temperature and poured into 100 ml of ice water containing 10 ml of concentrated hydrochloric acid. The resulting solution was adjusted to pH 5.0 by addition of 1N NaOH solution while stirring rapidly. The mixture was filtered and the residue was washed with 15 ml of water. The solid was dried in vacuo to give the product.

$^1\text{H}$  NMR ( $\text{CDCl}_3$  300 MHz): 7.42-7.56 (m, 3H); 7.59-7.65 (m, 1H); 7.68 (d, 2H); 8.11 (dt, 2H); 8.69 (bd, 2H).

#### PREPARATIVE EXAMPLE 7



15

To 0.019 g (0.039 Mmol) of sodium cyanide in 2 ml of dry DMF at 30°C was added a solution of 4-chlorobenzaldehyde in 1.5 ml of DMF over 20 minutes. A thick slurry formed. After 30 minutes a solution of the product of preparative example 6 in 1.5 ml of DMF was added dropwise. The mixture was agitated and stirred for 3 hours. The mixture was diluted with 30 ml of water and extracted with ethyl acetate (2 x 15 ml). The organic phase was washed with brine (1 x 15 ml) and dried over  $\text{MgSO}_4$ . The mixture was filtered and the filtrate was concentrated in vacuo to give structure of Example 20 (an oil).

25

### PREPARATIVE EXAMPLE 8

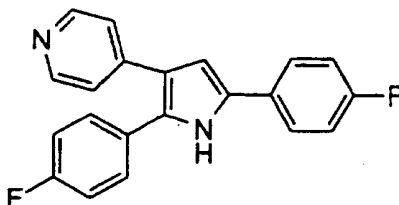
#### 1-phenyl-3-(4-pyridyl)-4-(4-methylthiophenyl)butan-1,4-dione

Using the procedure from Preparative Example 7 set forth  
5 above, substitute 4-methylthiobenzaldehyde for 4-chlorobenzaldehyde to  
produce the title compound.

### PREPARATIVE EXAMPLE 9

#### 2-(4-fluorophenyl)-3-(4-pyridyl)-5-(4-fluorophenyl)pyrrole

10



#### Method 1

To a solution of 0.35 g (0.99 mmol) of the compound of  
15 Preparative Example 5 in 15 mL of glacial acetic acid was added 0.35  
g (4.7 mmol) ammonium acetate. The mixture was heated to 90°C over  
10 hours at which time a further 1 g of ammonium acetate was added.  
Heating was continued at 110°C for 6 hours. The reaction mixture was  
concentrated to 50% of the original volume, and 25 mL of water was  
20 gradually added. A solid formed, which was filtered and dried in vacuo  
to give the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub> 300 MHz): 6.61 (s, 1H);  
6.98-7.05 (m, 4H); 7.20 (dd, 2H); 7.33 (dd, 2H); 7.53 (dd, 2H); 8.29 (d,  
2H). FAB ms: 333 (M<sup>+</sup>+1).

#### 25 Method 2

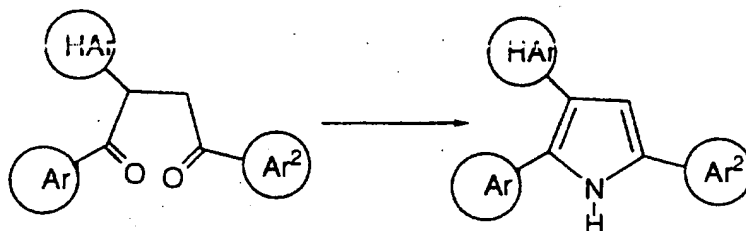
The condensation in method 1 was followed by an  
alternative work-up procedure. The reaction mixture was diluted with  
5 mL of water and extracted with ethyl acetate (3 x 4 mL). The organic  
extracts were dried over MgSO<sub>4</sub>, filtered and the filtrate was concentrated



in vacuo. The residue was purified by rotary chromatography to give the desired product.

### PREPARATIVE EXAMPLE 10-83

5



0.15-0.2 g of the 1,4 diketone above is dissolved in 3 mL of acetic acid to which is added 1.0 g of ammonium acetate. The mixture is heated at 110°C for 1.5-10 hours, and the compound is worked up as previously described to produce the compounds listed below in Table I.

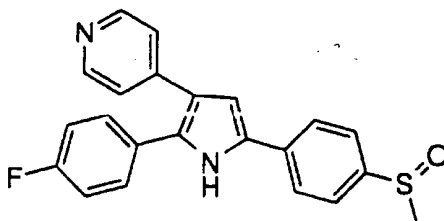
TABLE I

Preparative Example	Ar <sup>2</sup>	Ar <sup>1</sup>	HAr	FAB ms M <sup>+</sup> +1
10	Ph-4-OMe	Ph-4-F	4-Pyridyl	345
11	Ph-2,5-OMe	Ph-4-F	4-Pyridyl	375
12	Ph-4-Br	Ph-4-F	4-Pyridyl	393/395
13	Ph-4-Cl	Ph-4-F	4-Pyridyl	349
14	Ph-4-OMe	Ph-4-F	2-Pyridyl	345
15	Ph-4-Br	Ph-4-F	2-Pyridyl	393/395
16	Ph-4-Cl	Ph-4-F	2-Pyridyl	349
17	Ph-2,5-OMe	Ph-4-F	2-Pyridyl	375
18	Ph-4-OMe	Ph	4-Pyridyl	327
19	Ph-4-Cl	Ph	4-Pyridyl	331
20	Ph-2,5-OMe	Ph	4-Pyridyl	357
21	Ph-4-F	Ph	4-Pyridyl	315
22	Ph	Ph-4-Cl	4-Pyridyl	

23	Ph-4-SMe	Ph-4-F	4-Pyridyl	361
24	Ph	Ph-4-SMe	4-Pyridyl	
25	Ph-4-F	Ph	3-Pyridyl	
26	Ph-4-F	Ph	2-methyl-4-pyridyl	
27	Ph-4-F	Ph	3-methyl-4-pyridyl	
28	Ph-4-F	Ph	3,5-dimethyl-4-pyridyl	
29	Ph-4-F	Ph	3-quinolinyl	
30	Ph-4-F	Ph	4-quinolinyl	
31	Ph-4-F	Ph	2-quinolinyl	
32	Ph-4-F	Ph	2-pyrimidinyl	
33	Ph-4-F	Ph	4-pyrimidinyl	
34	Ph-4-F	Ph	3-pyridazinyl	
35	Ph-4-F	Ph	2-pyrazinyl	
36	Ph-4-F	Ph	2-pyrimidinyl	
37	Ph-4-F	Ph	4-pyrimidinyl	
38	Ph-4-F	Ph	2-imidazo-(4,5-b)-pyridinyl	
39	Ph-4-F	Ph	7-imidazo-(4,3-b)-pyridinyl	
40	Ph-4-F	Ph	4-Pyridyl	
41	Ph-4-F	Ph	4-Pyridyl	
42	Ph-4-CN	Ph	4-Pyridyl	
43	Ph-2-OMe	Ph	4-Pyridyl	
44	Ph-3-OMe	Ph	4-Pyridyl	
45	Ph-4-OMe	Ph	4-Pyridyl	
46	Ph-4-NO <sub>2</sub>	Ph	4-Pyridyl	
47	Ph-4-NMe <sub>2</sub>	Ph	4-Pyridyl	
48	Ph-4-(4-N-COCH <sub>3</sub> )-piperazinyl	Ph	4-Pyridyl	
49	Ph-4-morpholinyl	Ph	4-Pyridyl	
50	Ph-2-Cl	Ph	4-Pyridyl	
51	Ph-3-Cl	Ph	4-Pyridyl	

52	Ph-4-CF <sub>3</sub>	Ph	4-Pyridyl
53	Ph-4-S-Me	Ph	4-Pyridyl
54	Ph-4-S(O)-Me	Ph	4-Pyridyl
55	(4-methyl)-2-thiophenyl	Ph-4-F	4-Pyridyl
56	(3-methyl)-2-thiophenyl	Ph-4-F	4-Pyridyl
57	(4-bromo)-2-thiophenyl	Ph-4-F	4-Pyridyl
58	(5-methyl)-2-thiophenyl	Ph-4-F	4-Pyridyl
59	Ph-4-F-3-Cl	Ph-4-F	4-Pyridyl
60	2-benzoxazolyl	Ph-4-F	4-Pyridyl
61	2-benzofuranyl	Ph-4-F	4-Pyridyl
62	4-(O(CH <sub>2</sub> ) <sub>3</sub> NMe <sub>2</sub> )-Ph	Ph-4-F	4-Pyridyl
63	4-(O(CH <sub>2</sub> ) <sub>2</sub> N-piperidinyl)-Ph	Ph-4-F	4-Pyridyl
64	Ph-4-F	Ph-4-Cl	4-Pyridyl
65	Ph-4-F	Ph-3-Cl	4-Pyridyl
66	Ph-4-F	Ph-2-Cl	4-Pyridyl
67	Ph-4-F	Ph-3,4-Cl	4-Pyridyl
68	Ph-4-F	Ph-3-CF <sub>3</sub>	4-Pyridyl
69	Ph-4-F	Ph-4-S-Me	4-Pyridyl
70	Ph-4-F	Ph-4-S(O)-Me	4-Pyridyl
71	Ph-4-F	Ph-2-OBn	4-Pyridyl
72	Ph-4-F	Ph-4-Br	4-Pyridyl
73	Ph-4-F	Ph-2-OMe	4-Pyridyl
74	Ph-4-F	Ph-3-OMe	4-Pyridyl
75	Ph-4-F	Ph-4-OMe	4-Pyridyl
76	Ph-4-F	Ph-4-NO <sub>2</sub>	4-Pyridyl
77	Ph-4-F	Ph-4-NMe <sub>2</sub>	4-Pyridyl
78	Ph-4-F	Ph-4-(4-N-COCH <sub>3</sub> )-piperazinyl	4-Pyridyl
79	Ph-4-F	Ph-4-morpholinyl	4-Pyridyl

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PREPARATIVE EXAMPLE 80

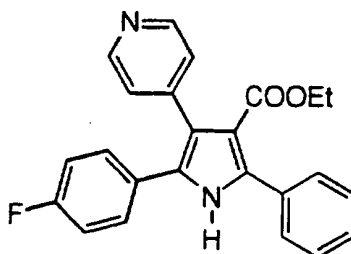
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To a solution of the compound of Preparative Example 3 above (55.5 mg (0.15 mmol) in 2 ml of acetic acid and 1.4 ml of water was added potassium persulfate (50.0 mg (0.18 mmol). After stirring for 1.5 hours at room temperature, the solution was neutralized by addition of ammonium hydroxide solution. The solid product was recovered by filtration and purified by flash chromatography eluting with 5% CH<sub>2</sub>Cl<sub>2</sub> to give the product.

10

FAB ms: Calc.: 376 for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub>SOF; Obs.: 377 (M<sup>++</sup>1).

15

EXAMPLE 1

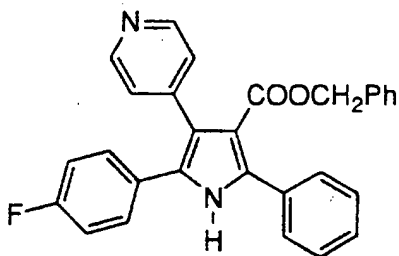
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A mixture of ethyl 2-benzoyl-acetate (0.41 g (2.0 mmol), 0.5 g (1.44 mmol) of the product of Preparative Example 2 and 0.61 g (8 mmol) of ammonium acetate were heated in acetic acid at reflux until the benzoin was consumed. The reaction mixture was diluted with ethyl acetate and washed with water and brine and dried over MgSO<sub>4</sub>. The

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mixture was filtered and the filtrate was concentrated in vacuo and the residue was purified by chromatography over silica gel to give the desired product.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300 MHz): 0.92 (t, 3H); 4.01 (q, 2H); 6.94 (t, 2H); 7.12 (m, 4H); 7.41 (m, 4H); 7.61 (m, 2H); 8.10 (m, 1H); 9.20 (bs, 1H). FAB ms:  $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2\text{F}$ =386; Observed:387 ( $\text{M}^+=1$ ).

### EXAMPLE 2

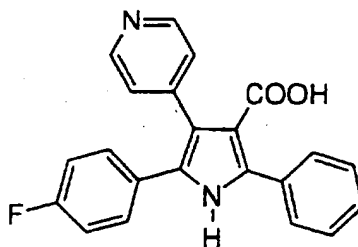


10

A mixture of benzyl 2-benzoyl-acetate (2.0 mmol), 0.5 g (1.44 mmol) of the product of Preparative Example 2 and 0.61 g (8 mmol) of ammonium acetate heated in acetic acid at reflux will provide the title compound after purification procedure stated in Example 2.

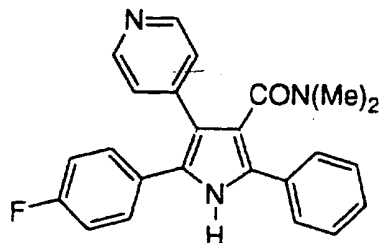
15

### EXAMPLE 3



20

A mixture of benzyl 2-(4-fluorophenyl)-3-(4-pyridyl)-5-phenylpyrrole-4-carboxylate from Example 2 (1.0 mmol), 0.01 g of 10% Pd/C in 5 mL of EtOH will yield 2-(4-fluorophenyl)-3-(4-pyridyl)-5-phenylpyrrole-4-carboxylic acid after treatment with 40 psi  $\text{H}_2$  followed by filtration.

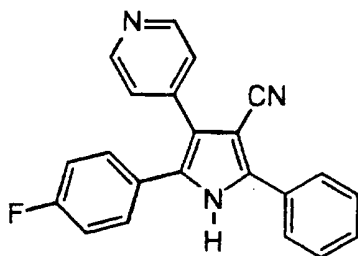
EXAMPLE 4

5

A mixture of 2-(4-fluorophenyl)-3-(4-pyridyl)-5-phenylpyrrole-4-carboxylic acid from Example 2 (1.0 mmol), EDC, Hunigs base and dimethylamine hydrochloride in DMF were stirred at room temperature over night. The reaction mixture was diluted with water  
10 adjusted to pH7.0 and extracted with ethyl acetate. The organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue was purified by chromatography.

EXAMPLE 5

15



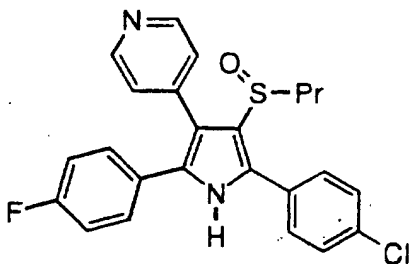
A mixture of benzoylacetonitrile 0.5 g (3.4 mmol),  
1.17 g (3.4 mmol) of the product of Example 2 and 1.0 g (13.6 mmol)  
20 ammonium acetate were heated in acetic acid at reflux until the benzoin was consumed. The reaction mixture was diluted with ethyl acetate and washed with water and brine and dried over  $\text{MgSO}_4$ . The mixture was filtered and the filtrate was concentrated in vacuo and the residue was

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purified by chromatography over silica gel eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to give the desired product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): 7.0 (t, 2H); 7.24 (m, 2H); 7.32-7.48 (m, 5-5H); 7.74 (bd, 2H); 8.42 (bs, 1H). FAB ms: C<sub>22</sub>H<sub>14</sub>N<sub>3</sub>F=339; Observed: 340 (M<sup>+</sup>=1).

### EXAMPLE 6

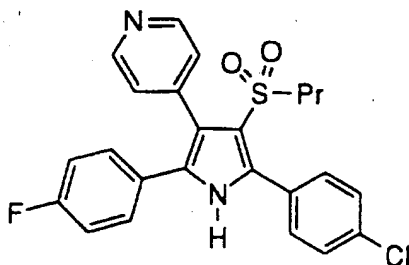


10

The product of Preparative Example 13 is dissolved in methylene chloride and treated with 1.05 equivalents of n-propylsulfinyl chloride at 0°C under nitrogen. After 30 minutes triethyl amine is added to neutralize the reaction mixture. The reaction mixture is diluted with ethyl acetate and washed with water and brine and dried over MgSO<sub>4</sub>. The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

20

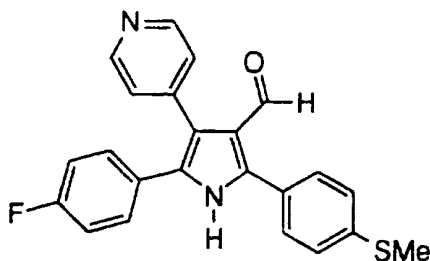
### EXAMPLE 7



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The product of Example 6 is reacted with 1.05 equivalents of meta-chloroperoxybenzoic acid in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ . The reaction mixture is stirred overnight at room temperature. The solution is diluted with EtOAc and washed with saturated sodium bicarbonate solution followed by brine. The solution is dried over  $\text{MgSO}_4$ , filtered and concentrated in vacuo. The residue is purified by silica gel chromatography to produce the desired product.

#### EXAMPLE 8



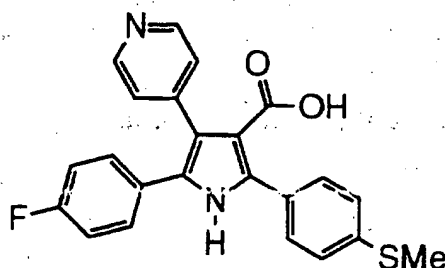
10

To 5 ml of DMF at room temperature under nitrogen is added 0.3 g (2 mmol) of  $\text{POCl}_3$  dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Preparative Example 23 is added dropwise. The solution was warmed at  $60^\circ\text{C}$  until the starting material had been consumed. The reaction mixture was cooled to room temperature and then poured into ice water (20 ml). The mixture was made basic by addition of saturated sodium carbonate solution and then stirred in the presence of 20 ml of chloroform. The chloroform phase was separated and the aqueous phase was extracted with chloroform (2 x 10 ml). The combined organic phase is washed with water and brine and dried over  $\text{MgSO}_4$ . The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

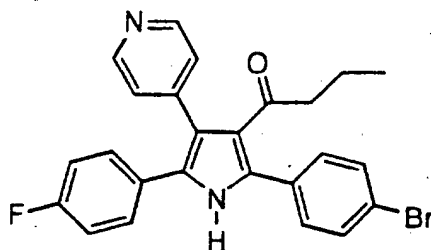
25



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EXAMPLE 9

- 5           The product of Example 8 is dissolved in t-butyl alcohol and methyl 2-butene (6:1 ratio). The solution is then treated with 1.5 eq of monobasic sodium phosphate and an aqueous solution of sodium chlorate. The reaction mixture is stirred at room temperature until the sm is consumed. The pH is adjusted to 5.5 with dilute HCl. The product is
- 10   extracted with ethyl acetate and the combined organic phase is washed with water and brine and dried over MgSO<sub>4</sub>. The mixture is filtered and the filtrate is concentrated in vacuo to give the desired product.

EXAMPLE 10

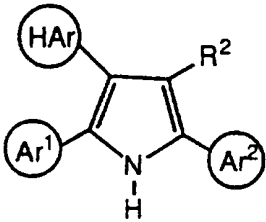
- 15           To 5 ml of N,N-dimethyl-butylamide at room temperature under nitrogen is added 0.3 g (2 mmol) of POCl<sub>3</sub> dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Preparative
- 20   Example 15 is added dropwise. The solution is warmed at 60°C until the starting material is consumed. The reaction mixture is cooled to room temperature and then poured into ice water (20 ml). The mixture is made basic by addition of saturated sodium carbonate solution and then stirred

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- in the presence of 20 mL of chloroform. The chloroform phase is separated and the aqueous phase extracted with chloroform (2 x 10 ml). The combined organic phase is washed with water and brine and dried over  $\text{MgSO}_4$ . The mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography over silica gel to give the desired product.
- 5

EXAMPLES 11-80

- 10 Using the procedures set forth above, the compounds shown in Table II can be prepared.

TABLE II				
				
Example	$(\text{R}^a)_a - \text{Ar}^1$	$\text{Ar}^2 - (\text{R}^a)_b$	$(\text{R}^a)_{0-3} - \text{HAr}$	$\text{R}^2$
11	Ph-4-F	Ph-4-OMe	4-pyridyl	C(O)Me
12	Ph-4-F	Ph-2,5-OMe	4-pyridyl	C(O)Me
13	Ph-4-F	Ph-4-Br	4-pyridyl	C(O)Propyl
14	Ph-4-F	Ph-4-Cl	4-pyridyl	C(O)Ethyl
15	Ph-4-F	Ph-4-OMe	2-pyridyl	C(O)Me
16	Ph-4-F	Ph-4-Br	2-pyridyl	C(O)Me
17	Ph-4-F	Ph-2,5-OMe	2-pyridyl	C(O)Me
18	Ph	Ph-4-OMe	4-pyridyl	C(O)Me
19	Ph	Ph-4-Cl	4-pyridyl	C(O)Me
20	Ph	Ph-2,5-OMe	4-pyridyl	C(O)Me
21	Ph	Ph-4-F	4-pyridyl	C(O)Me

22	Ph-4-Cl	Ph	4-pyridyl	C(O)Me
23	Ph-4-F	Ph-4-SMe	4-pyridyl	C(O)Me
24	Ph-4-SMe	Ph	3-methyl-4-pyridyl	C(O)Me
25	Ph-4-F	Ph-4-SMe	3-methyl-4-pyridyl	CN
26	Ph-4-F	Ph-4-S(O)Me	3-methyl-4-pyridyl	CN
27	Ph-3-Cl	Ph-4-Cl	4-quinolyl	CN
28	Ph-4-F	Ph-4-Cl	2-methyl-4-pyridyl	CN
29	Ph	Ph-4-F	3,5-dimethyl-4-pyridyl	CN
30	Ph	Ph-4-F	3-quinoliny	CN
31	Ph	Ph-4-F	4-quinoliny	CN
32	Ph	Ph-4-F	2-quinoliny	CN
33	Ph	Ph-4-F	2-pyrimidinyl	CN
34	Ph	Ph-4-F	4-pyrimidinyl	CN
35	Ph	Ph-4-F	3-pyridazinyl	CN
36	Ph	Ph-4-F	2-pyrazinyl	CN
37	Ph	Ph-4-F	2-pyrimidinyl	CN
38	Ph	Ph-4-F	4-pyrimidinyl	CN
39	Ph	Ph-4-F	2-imidazo-(4,5-b)-pyridinyl	CN
40	Ph	Ph-4-F	7-imidazo-(4,3-b)-pyridinyl	CN
41	Ph	Ph-4-F	4-pyridyl	COMe
42	Ph	Ph-4-F	4-pyridyl	SO2Me

43	Ph	Ph-4-CN	4-pyridyl	COMe
44	Ph	Ph-2-OMe	4-pyridyl	COMe
45	Ph	Ph-3-OMe	4-pyridyl	CN
46	Ph	Ph-4-OMe	4-pyridyl	CO <sub>2</sub> Et
47	Ph	Ph-4-NO <sub>2</sub>	4-pyridyl	CN
48	Ph	Ph-4-NMe <sub>2</sub>	4-pyridyl	CN
49	Ph	Ph-4-(4-N-COCH <sub>3</sub> )-piperazinyl	4-pyridyl	CN
50	Ph	Ph-4-morpholinyl	4-pyridyl	CN
51	Ph	Ph-2-Cl	4-pyridyl	CN
52	Ph	Ph-3-Cl	4-pyridyl	COMe
53	Ph	Ph-4-CF <sub>3</sub>	4-pyridyl	SO <sub>2</sub> Me
54	Ph	Ph-4-S-Me	4-pyridyl	CN
55	Ph	Ph-4-S(O)-Me	4-pyridyl	CN
56	Ph-4-F	(4-methyl)-2-thiophenyl	4-pyridyl	CN
57	Ph-4-F	(3-methyl)-2-thiophenyl	4-pyridyl	COMe
58	Ph-4-F	(4-bromo)-2-thiophenyl	4-pyridyl	SO <sub>2</sub> Me
59	Ph-4-F	(5-methyl)-2-thiophenyl	4-pyridyl	CN
60	Ph-4-F	Ph-4-F-3-Cl	4-pyridyl	CN
61	Ph-4-F	2-benzoxazolyl	4-pyridyl	CN
62	Ph-4-F	2-benzofuranyl	4-pyridyl	CN
63	Ph-4-F	4-(O(CH <sub>2</sub> ) <sub>3</sub> NMe <sub>2</sub> )-Ph	4-pyridyl	CN

64	Ph-4-F	4-(O(CH <sub>2</sub> ) <sub>2</sub> N-piperidinyl)-Ph	4-pyridyl	CN
65	Ph-4-Cl	Ph-4-F	4-pyridyl	CN
66	Ph-3-Cl	Ph-4-F	4-pyridyl	CN
67	Ph-2-Cl	Ph-4-F	4-pyridyl	CN
68	Ph-3,4-Cl	Ph-4-F	4-pyridyl	CN
69	Ph-3-CF <sub>3</sub>	Ph-4-F	4-pyridyl	CN
70	Ph-4-S-Me	Ph-4-F	4-pyridyl	CN
71	Ph-4-S(O)-Me	Ph-4-F	4-pyridyl	CN
72	Ph-2-OBn	Ph-4-F	4-pyridyl	CN
73	Ph-4-Br	Ph-4-F	4-pyridyl	CN
74	Ph-2-OMe	Ph-4-F	4-pyridyl	CN
75	Ph-3-OMe	Ph-4-F	4-pyridyl	CN
76	Ph-4-OMe	Ph-4-F	4-pyridyl	CN
77	Ph-4-NO <sub>2</sub>	Ph-4-F	4-pyridyl	CN
787	Ph-4-NMe <sub>2</sub>	Ph-4-F	4-pyridyl	CN
79	Ph-4-(4-N-COCH <sub>3</sub> )-piperazinyl	Ph-4-F	4-pyridyl	CN
80	Ph-4-morpholinyl	Ph-4-F	4-pyridyl	CN

### BIOLOGICAL ASSAYS

The ability of compounds of the present invention to inhibit the synthesis or the activity of cytokines were determined by the following *in vitro* assays.

#### Lipopolysaccharide mediated production of cytokines

Human peripheral blood mononuclear cells (PBMC) are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin

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(Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and  
5 then resuspended to a final concentration of  $2 \times 10^6$  cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Lipopolysaccharide (Salmonella type Re545; Sigma Chemicals) is added to the cells to a final concentration of 100 ng/mL. An aliquot (0.1 mL) of the cells is quickly dispensed into  
10 each well of a 96 well plate containing 0.1 mL of the test compound, at the appropriate dilution, and are incubated for 24 hours. at 37°C in 5% CO<sub>2</sub>. At the end of the culture period, cell culture supernatants are assayed for IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and PGE<sub>2</sub> production using specific ELISA.

15

#### IL-1 mediated cytokine production

Human peripheral blood mononuclear cells are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile  
20 venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and  
25 then resuspended to a final concentration of  $2 \times 10^6$  cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Endotoxin free recombinant human IL-1 $\beta$  is then added to a final concentration of 50 pMolar. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate  
30 containing 0.1 mL of the compound at the appropriate dilution. and are incubated for 24 hours. at 37°C in 5% CO<sub>2</sub>. At the end of the culture period, cell culture supernatants are assayed for TNF- $\alpha$ , IL-6 and PGE<sub>2</sub> synthesis using specific ELISA.

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Determination of IL-1 $\beta$ , TNF- $\alpha$ , IL-6 and prostanoid production from LPS or IL-1 stimulated PBMC's

IL-1 $\beta$  ELISA

- 5 Human IL-1 $\beta$  can be detected in cell-culture supernatants or whole blood with the following specific trapping ELISA. Ninety-six well plastic plates (Immulon 4; Dynatech) are coated for 12 hours at 4°C with 1 mg/mL protein-A affinity chromatography purified mouse anti-human IL-1b monoclonal antibody (purchased as an ascites preparation from
- 10 LAO Enterprise, Gaithersburg Maryland.) diluted in Dulbecco's phosphate-buffered saline (-MgCl<sub>2</sub>, -CaCl<sub>2</sub>). The plates are washed with PBS-Tween (Kirkegaard and Perry) then blocked with 1% BSA diluent and blocking solution (Kirkegaard and Perry) for 60 minutes at room temperature followed by washing with PBS Tween. IL-1 $\beta$  standards are
- 15 prepared from purified recombinant IL-1 $\beta$  produced from *E. coli*. The highest concentration begins at 10 ng/mL followed by 11 two-fold serial dilutions. For detection of IL-1 $\beta$  from cell culture supernatants or blood plasma, 10 - 25 mL of supernatant is added to each test well with 75 - 90 mL of PBS Tween. Samples are incubated at room temperature for 2
- 20 hours then washed 6 times with PBS Tween on an automated plate washer (Dennly). Rabbit anti-human IL-1 $\beta$  polyclonal antisera diluted 1:500 in PBS-Tween is added to the plate and incubated for 1 hour at room temperature followed by six washes with PBS-Tween. Detection of bound rabbit anti-IL-1 $\beta$  IgG is accomplished with Fab' fragments of
- 25 Goat anti-rabbit IgG-horseradish peroxidase conjugate (Accurate Scientific) diluted 1:10,000 in PBS-Tween. Peroxidase activity was determined using TMB peroxidase substrate kit (Kirkegaard and Perry) with quantitation of color intensity on a 96-well plate Molecular Devices spectrophotometer set to determine absorbance at 450 nM. Samples are
- 30 evaluated using a standard curve of absorbance versus concentration. Four-parameter logistics analysis generally is used to fit data and obtain concentrations of unknown compounds.

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TNF- $\alpha$  ELISA

Immulon 4 (Dynatech) 96-well plastic plates are coated with a 0.5 mg/mL solution of mouse anti-human TNF- $\alpha$  monoclonal antibody. The secondary antibody is a 1:2500 dilution of a rabbit anti-human TNF- $\alpha$  polyclonal serum purchased from Genzyme. All other operations are identical to those described above for IL-1 $\beta$ . The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 20 ng/mL TNF- $\alpha$ .

10 IL-6 ELISA

Levels of secreted human IL-6 are also determined by specific trapping ELISA as described previously in Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). (Dynatech) ELISA plates are coated with mouse anti-human IL-6 monoclonal antibody diluted to 0.5 mg/ml in PBS. The secondary antibody, a rabbit anti-human IL-6 polyclonal antiserum, is diluted 1:5000 with PBS-Tween. All other operations are identical to those described above for IL-1 $\beta$ . The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 50 ng/mL IL-6.

20

PGE<sub>2</sub> production

Prostaglandin E<sub>2</sub> is detected in cell culture supernatants from LPS or IL-1 stimulated PBMC's using a commercially available enzyme immunoassay. The assay purchased from the Cayman Chemical (Catalogue number 514010) and is run exactly according to the manufacturers instructions.

25 Interleukin 8 (IL-8)

The present compounds can also be assayed for IL-8 inhibitory activity as discussed below. Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of  $\alpha$ FGF and heparin. The cells are then diluted 20-fold before being plated (250  $\mu$ l) into gelatin coated 96-well plates. Prior

30



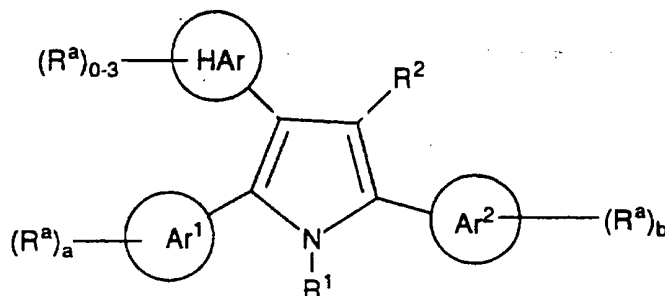
- 63 -

- 5 to use, culture medium is replaced with fresh medium (200 $\mu$ l). Buffer or test compound (25 $\mu$ l, at appropriate concentrations) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO<sub>2</sub>. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC50 values where appropriate are generated by non-linear regression analysis.

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WHAT IS CLAIMED IS:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof,

wherein:



represents a 5-10 membered aryl group;



represent a 5-10 membered aryl or heteroaryl group;

15 a and b represents integers, 0, 1, 2 or 3, such that the sum of a plus b is 1, 2, 3 or 4;



20 represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1-3  $R^a$  groups;

each  $R^a$  independently represents a member selected from the group consisting of: halo; CN, NO<sub>2</sub>, R<sup>21</sup>, OR<sup>23</sup>, SR<sup>23</sup>, S(O)R<sup>21</sup>, SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>,  
 25 NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>C(NR<sup>20</sup>)NHR<sup>23</sup>, CO<sub>2</sub>R<sup>23</sup>, CONR<sup>20</sup>R<sup>23</sup>,

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SO<sub>2</sub>NR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>,  
 SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, OCONR<sup>20</sup>R<sup>23</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>20</sup>,  
 C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup>, C(NR<sup>20</sup>)NR<sup>20</sup>R<sup>23</sup>, C(O)NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup> and  
 tetrazol-5-yl;

5 R<sup>1</sup> is selected from the group consisting of: H, C<sub>1-15</sub> alkyl,  
 C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, aryl and heterocyclyl, said alkyl, alkenyl,  
 alkynyl, aryl and heterocyclyl being optionally substituted with from one  
 to three members selected from the group consisting of: aryl, heteroaryl,  
 10 heterocyclyl, OR<sup>20</sup>, SR<sup>20</sup>, N(R<sup>20</sup>)<sub>2</sub>, S(O)R<sup>21</sup>, SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>23</sup>,  
 SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>,  
 NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, N(R<sup>20</sup>)C(NR<sup>20</sup>)NHR<sup>20</sup>, CO<sub>2</sub>R<sup>20</sup>, CON(R<sup>20</sup>)<sub>2</sub>,  
 CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, OCONR<sup>20</sup>R<sup>23</sup>,  
 OCONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup> and OCONR<sup>20</sup>R<sup>23</sup>;

15 R<sup>2</sup> is selected from the group consisting of: CN, S(O)R<sup>21</sup>,  
 SO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>N(R<sup>20</sup>)<sub>2</sub>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CON(R<sup>20</sup>)<sub>2</sub>, COR<sup>20</sup>,  
 CO<sub>2</sub>R<sup>20</sup>, CONR<sup>20</sup>R<sup>23</sup>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup> and SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>;

20 R<sup>20</sup> represents a member selected from the group consisting  
 of: H, C<sub>1-15</sub> alkyl, C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, heterocyclyl, aryl and  
 heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted  
 with 1-3 groups selected from halo, aryl and heteroaryl;

25 R<sup>21</sup> represents a member selected from the group consisting  
 of: C<sub>1-15</sub> alkyl, C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, heterocyclyl, aryl and  
 heteroaryl, said alkyl, alkenyl and alkynyl being optionally interrupted by  
 1-2 heteroatoms selected from O, S, S(O), SO<sub>2</sub> and NR<sup>20</sup>, said alkyl,  
 alkenyl, alkynyl, heterocyclyl, aryl and heteroaryl being optionally  
 30 substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN,  
 OR<sup>20</sup>, C(O)R<sup>20</sup>, O((CH<sub>2</sub>)<sub>n</sub>O)<sub>m</sub>R<sup>20</sup>, NR<sup>20</sup>((CH<sub>2</sub>)<sub>n</sub>O)<sub>m</sub>R<sup>20</sup> wherein n  
 represents an integer of from 2 to 4, and m represents an integer of from 1  
 to 3; SR<sup>20</sup>, N(R<sup>20</sup>)<sub>2</sub>, S(O)R<sup>22</sup>, SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>N(R<sup>20</sup>)<sub>2</sub>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>22</sup>,  
 SO<sub>2</sub>NR<sup>20</sup>CON(R<sup>20</sup>)<sub>2</sub>, NR<sup>20</sup>COR<sup>22</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>22</sup>, NR<sup>20</sup>CON(R<sup>20</sup>)<sub>2</sub>,

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NR<sup>22</sup>C(NR<sup>22</sup>)NHR<sup>22</sup>, CO<sub>2</sub>R<sup>20</sup>, CON(R<sup>20</sup>)<sub>2</sub>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>22</sup>,  
NR<sup>20</sup>SO<sub>2</sub>R<sup>22</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>22</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>22</sup> OC(O)R<sup>20</sup>,  
C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup>, OC(O)NR<sup>20</sup>R<sup>23</sup> and OCON(R<sup>20</sup>)<sub>2</sub>;

5                   R<sup>22</sup> is selected from the group consisting of: C<sub>1-15</sub> alkyl,  
C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl,  
alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or  
heteroaryl groups;

10                   R<sup>23</sup> is R<sup>21</sup> or H;

                  R<sup>24</sup> is selected from COR<sup>22</sup>, CO<sub>2</sub>R<sup>22</sup>, CON(R<sup>20</sup>)<sub>2</sub>,  
SO<sub>2</sub>R<sup>22</sup> and R<sup>23</sup>;

15                   and in a functional group when two R<sup>20</sup> groups are present,  
when R<sup>20</sup> and R<sup>21</sup> are present, or when R<sup>20</sup> and R<sup>23</sup> are present, said  
two R<sup>20</sup> groups, R<sup>20</sup> and R<sup>21</sup> or said R<sup>20</sup> and R<sup>23</sup> may be taken in  
combination with the atoms to which they are attached and any  
intervening atoms and represent heterocyclyl containing from 5-10  
20                  atoms, at least one atom of which is a heteroatom selected from O, S or  
N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1  
additional O or S atom.

2.           A compound in accordance with claim 1 wherein Ar<sup>1</sup>  
25           represents a phenyl or naphthyl group;

                  and Ar<sup>2</sup> is selected from the group consisting of:

- 30                   a) phenyl,  
                  b) pyridyl,  
                  c) pyrimidinyl,  
                  d) thiophenyl,  
                  e) furanyl,  
                  f) imidazolyl,  
                  g) thiazolyl,

- 67 -

h) isothiazolyl,

i) oxazolyl,

j) isoxazolyl and

k) naphthyl.

5

3. A compound in accordance with claim 1 wherein HAr is selected from the group consisting of:

10

a) pyridyl,

b) quinolyl,

c) purinyl,

d) imidazolyl,

e) imidazopyridine and

f) pyrimidinyl.

15

4. A compound in accordance with claim 1 wherein R<sup>1</sup> represents hydrogen.

20

5. A compound in accordance with claim 1 wherein R<sup>1</sup> represents substituted or unsubstituted C<sub>1-15</sub> alkyl

25

6. A compound in accordance with claim 1 wherein R<sup>2</sup> represents a member selected from the group consisting of:

a) CN;

b) C(O)C<sub>1-6</sub> alkyl;c) C(O)C<sub>1-6</sub> alkylphenyl;d) CO<sub>2</sub>H;e) CO<sub>2</sub>C<sub>1-6</sub> alkylf) CO<sub>2</sub>C<sub>1-6</sub> alkylphenyl;g) CONH<sub>2</sub>;

30

h) CONHC<sub>1-6</sub> alkyl;i) C(O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>;j) SO<sub>2</sub>NH<sub>2</sub>;k) SO<sub>2</sub>NHC<sub>1-6</sub> alkyl andl) SO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>.

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7. A compound in accordance with claim 2 wherein Ar<sup>1</sup> represents phenyl or naphthyl; Ar<sup>2</sup> is selected from the group consisting of:

5

- a) phenyl,
- b) pyridyl,
- c) pyrimidinyl,
- d) thiophenyl,
- 10 e) furanyl,
- f) imidazolyl,
- g) thiazolyl,
- h) isothiazolyl,
- i) oxazolyl,
- 15 j) isoxazolyl and
- k) naphthyl;

one, two or three R<sup>a</sup> groups are present, and each R<sup>a</sup> is independently selected from the group consisting of: halo, R<sup>21</sup>, OR<sup>23</sup>,  
20 NR<sup>20</sup>R<sup>23</sup>, CO<sub>2</sub>R<sup>23</sup>, CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>R<sup>21</sup> and S(O)R<sup>21</sup>;

HAr is selected from the group consisting of:

- a) pyridyl,
- 25 b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- e) imidazopyridine and
- f) pyrimidinyl;

30

R<sup>1</sup> is:

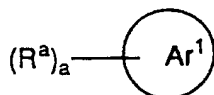
- a) H or
- b) substituted or unsubstituted C<sub>1-6</sub> alkyl; and

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and R<sup>2</sup> is selected from the group consisting of:

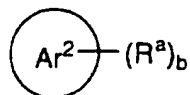
- 5        —        a) CN;  
                  b) C(O)C<sub>1-6</sub> alkyl;  
                  c) C(O)C<sub>1-6</sub> alkylphenyl;  
                  d) CO<sub>2</sub>H;  
                  e) CO<sub>2</sub>C<sub>1-6</sub> alkyl;  
                  f) CO<sub>2</sub>C<sub>1-6</sub> alkylphenyl;  
                  g) CONH<sub>2</sub>;  
                  h) CONHC<sub>1-6</sub> alkyl;  
 10        i) C(O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>;  
                  j) SO<sub>2</sub>NH<sub>2</sub>;  
                  k) SO<sub>2</sub>NHC<sub>1-6</sub> alkyl and  
                  l) SO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>.

- 15        8.        A compound in accordance with claim 1 wherein:



is selected from the group consisting of:

- 20        a) phenyl,  
                  b) 4-fluorophenyl,  
                  c) 4-chlorophenyl,  
                  d) 3-fluorophenyl,  
                  e) 3-chlorophenyl,  
                  f) 3-methyl phenyl,  
                  g) 3,4 dichlorophenyl, and  
 25        h) 3-hydroxyphenyl;



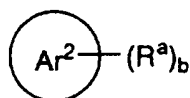
is selected from the group consisting of:

- 30        a) 4-methylthiophenyl,  
                  b) 4-ethylthiophenyl,

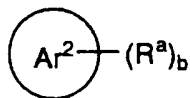
- 70 -

- 5 c) 3-methylthiophenyl,  
 d) 2-methylthiophenyl,  
 e) 3-ethylthiophenyl,  
 f) 4-methylsulfonylphenyl,  
 g) 4-ethylsulfonylphenyl,  
 h) 3-methylsulfonylphenyl,  
 i) 2-methylsulfonylphenyl,  
 j) 4-methylsulfinylphenyl,  
 k) 4-ethylsulfonylphenyl,  
 10 l) 3-methylsulfinylphenyl,  
 m) 4-(N-methyl-N-benzyl)aminomethylphenyl,  
 n) 3-(N-methyl-N-benzyl)aminomethylphenyl,  
 o) 4-methoxyphenyl,  
 p) 4-hydroxyphenyl,  
 15 q) 3-methoxyphenyl,  
 r) 2-benzyloxyphenyl,  
 s) 4-methylthiophen-2-yl,  
 t) 4-methylthiophen-3-yl,  
 u) 4-acetylamino-phenyl, and  
 20 v) 2-pyrimidinyl;

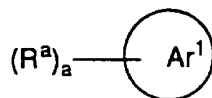
with the proviso that when  $(R^a)_a - \text{Ar}^1$  represents a),



represents one of a) through u); and when



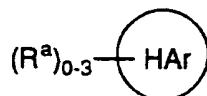
represents v),



represents one of b)

through h);

25



is selected from the group consisting of:

- a) 4-pyridyl,



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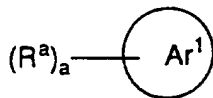
- 5
- b) 4-(2-methylpyridyl),
  - c) 4-(2-aminopyridyl),
  - d) 4-(2-methoxypyridyl),
  - e) 4-quinolyl,
  - f) 4-pyrimidinyl,
  - g) 9-purinyl,
  - h) 7-(imidazo[4,5-b]pyridinyl), and
  - i) 4-(3-methylpyridyl);

10  $R^1$  is H; and

$R^2$  is selected from the group consisting of:

- 15
- a) CN;
  - b)  $C(O)C_{1-6}$  alkyl;
  - c)  $C(O)C_{1-6}$  alkylphenyl;
  - d)  $CO_2H$ ;
  - e)  $CO_2C_{1-6}$  alkyl
  - f)  $CO_2C_{1-6}$  alkylphenyl;
  - g)  $CONH_2$ ;
  - h)  $CONHC_{1-6}$  alkyl;
  - 20 i)  $C(O)N(C_{1-6} \text{ alkyl})_2$ ;
  - j)  $SO_2NH_2$ ;
  - k)  $SO_2NHC_{1-6}$  alkyl and
  - l)  $SO_2N(C_{1-6} \text{ alkyl})_2$ .

25 9. A compound in accordance with claim 1 wherein:

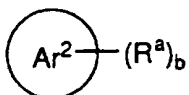


is selected from the group consisting of

- 30
- a) phenyl,
  - b) 4-fluorophenyl,
  - c) 4-chlorophenyl,
  - d) 3-fluorophenyl,
  - e) 3-chlorophenyl,

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- 5 — f) thiophen-2-yl,  
 g) thiophen-3-yl,  
 h) 4-fluorothiophen-2-yl,  
 i) 4-fluorothiophen-3-yl,  
 j) 5-fluorothiophen-2-yl,  
 k) 5-fluorothiophen-3-yl,  
 l) 4-chlorothiophen-2-yl,  
 m) 4-chlorothiophen-3-yl,  
 10 n) 5-chlorothiophen-2-yl,  
 o) 5-chlorothiophen-3-yl,  
 p) 3-methyl phenyl,  
 q) 3,4 dichlorophenyl, and  
 r) 3-hydroxyphenyl;



is selected from the group consisting of:

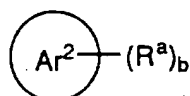
- 15 a) 4-methylthiophenyl,  
 b) 4-ethylthiophenyl,  
 c) 3-methylthiophenyl,  
 d) 2-methylthiophenyl,  
 e) 3-ethylthiophenyl,  
 20 f) 4-methylsulfonylphenyl,  
 g) 4-ethylsulfonylphenyl,  
 h) 3-methylsulfonylphenyl,  
 i) 2-methylsulfonylphenyl,  
 j) 4-methylsulfinylphenyl,  
 25 k) 4-ethylsulfonylphenyl,  
 l) 3-methylsulfinylphenyl,  
 m) 4-(N-methyl-N-benzyl)aminomethylphenyl,  
 n) 3-(N-methyl-N-benzyl)aminomethylphenyl,  
 o) 4-methoxyphenyl,  
 30 p) 4-hydroxyphenyl,  
 q) 3-methoxyphenyl,  
 r) 2-benzyloxyphenyl,

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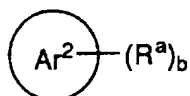
- s) 4-methylthiophen-2-yl,  
 t) 4-methylthiophen-3-yl,  
 u) 4-acetylamino-phenyl, and  
 v) 2-pyrimidinyl;

5

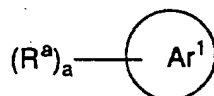
with the proviso that when  $(R^a)_a - \text{Ar}^1$  represents a),



represents one of a) through u); and when

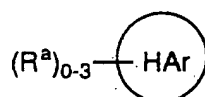


represents v),



represents one of b)

through h);



10

is selected from the group consisting of:

- a) 4-pyridyl,  
 b) 4-(2-methylpyridyl),  
 c) 4-(2-aminopyridyl),  
 d) 4-(2-methoxypyridyl),  
 e) 4-quinolyl,  
 f) 4-pyrimidinyl,  
 g) 9-purinyl,  
 h) 7-(imidazo[4,5-b]pyridinyl) and  
 i) 4-(3-methylpyridyl);

15

20

$R^1$  is substituted or unsubstituted  $C_{1-15}$  alkyl; and

$R^2$  is selected from the group consisting of:

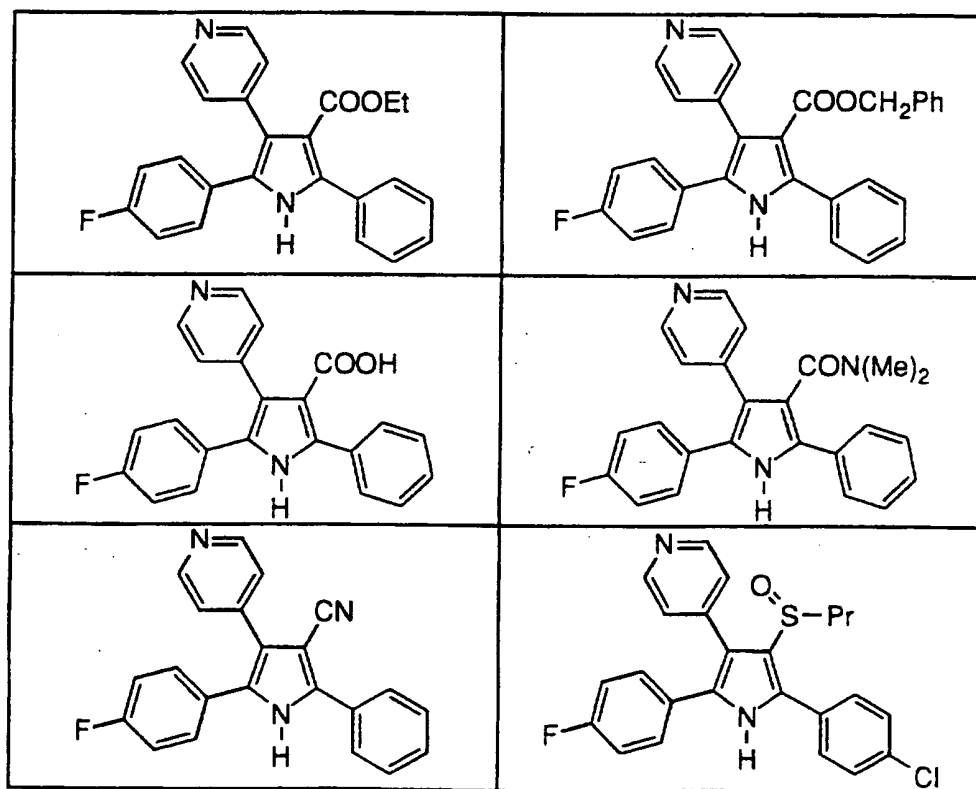
25

- a) CN;  
 b)  $C(O)C_{1-6}$  alkyl;  
 c)  $C(O)C_{1-6}$  alkylphenyl;  
 d)  $CO_2H$ ;

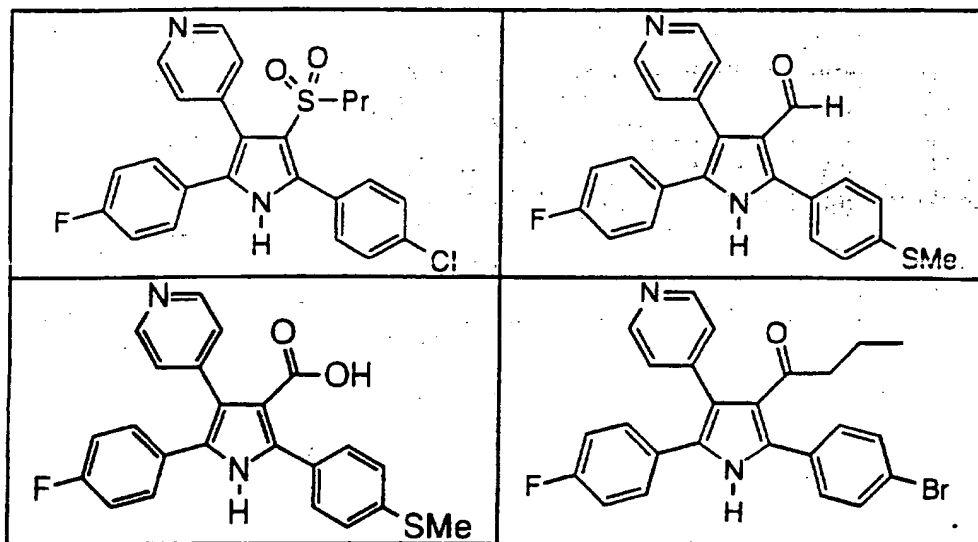
- 74 -

- 5 e)  $\text{CO}_2\text{C}_{1-6}$  alkyl;  
f)  $\text{CO}_2\text{C}_{1-6}$  alkylphenyl;  
g)  $\text{CONH}_2$ ;  
h)  $\text{CONHC}_{1-6}$  alkyl;  
i)  $\text{C(O)N(C}_{1-6}\text{ alkyl)}_2$ ;  
j)  $\text{SO}_2\text{NH}_2$ ;  
k)  $\text{SO}_2\text{NHC}_{1-6}$  alkyl and  
l)  $\text{SO}_2\text{N(C}_{1-6}\text{ alkyl)}_2$ .

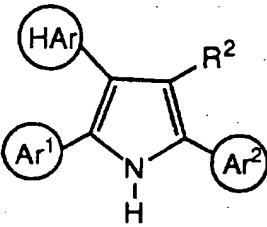
- 10 10. A compound in accordance with claim 1 represented by the formula:



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11. A compound in accordance with claim 1 selected from Table II:

TABLE II			
			
$(R^a)_a - \text{Ar}^1$	$\text{Ar}^2 - (R^a)_b$	$(R^a)_{0-3} - \text{HAr}$	$R^2$
Ph-4-F	Ph-4-OMe	4-pyridyl	C(O)Me
Ph-4-F	Ph-2,5-OMe	4-pyridyl	C(O)Me
Ph-4-F	Ph-4-Br	4-pyridyl	C(O)Propyl
Ph-4-F	Ph-4-Cl	4-pyridyl	C(O)Ethyl
Ph-4-F	Ph-4-OMe	2-pyridyl	C(O)Me
Ph-4-F	Ph-4-Br	2-pyridyl	C(O)Me

Ph-4-F	Ph-2,5-OMe	2-pyridyl	C(O)Me
Ph	Ph-4-OMe	4-pyridyl	C(O)Me
Ph	Ph-4-Cl	4-pyridyl	C(O)Me
Ph	Ph-2,5-OMe	4-pyridyl	C(O)Me
Ph	Ph-4-F	4-pyridyl	C(O)Me
Ph-4-Cl	Ph	4-pyridyl	C(O)Me
Ph-4-F	Ph-4-SMe	4-pyridyl	C(O)Me
Ph-4-SMe	Ph	3-methyl-4-pyridyl	C(O)Me
Ph-4-F	Ph-4-SMe	3-methyl-4-pyridyl	CN
Ph-4-F	Ph-4-S(O)Me	3-methyl-4-pyridyl	CN
Ph-3-Cl	Ph-4-Cl	4-quinolyl	CN
Ph-4-F	Ph-4-Cl	2-methyl-4-pyridyl	CN
Ph	Ph-4-F	3,5-dimethyl-4-pyridyl	CN
Ph	Ph-4-F	3-quinoliny	CN
Ph	Ph-4-F	4-quinoliny	CN
Ph	Ph-4-F	2-quinoliny	CN
Ph	Ph-4-F	2-pyrimidinyl	CN
Ph	Ph-4-F	4-pyrimidinyl	CN
Ph	Ph-4-F	3-pyridazinyl	CN
Ph	Ph-4-F	2-pyrazinyl	CN
Ph	Ph-4-F	2-pyrimidinyl	CN
Ph	Ph-4-F	4-pyrimidinyl	CN
Ph	Ph-4-F	2-imidazo-(4,5-b)-pyridinyl	CN

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Ph	Ph-4-F	7-imidazo- (4,3-b)- pyridinyl	CN
Ph	Ph-4-F	4-pyridyl	COMe
Ph	Ph-4-F	4-pyridyl	SO <sub>2</sub> Me
Ph	Ph-4-CN	4-pyridyl	COMe
Ph	Ph-2-OMe	4-pyridyl	COMe
Ph	Ph-3-OMe	4-pyridyl	CN
Ph	Ph-4-OMe	4-pyridyl	CO <sub>2</sub> Et
Ph	Ph-4-NO <sub>2</sub>	4-pyridyl	CN
Ph	Ph-4-NMe <sub>2</sub>	4-pyridyl	CN
Ph	Ph-4-(4-N- COCH <sub>3</sub> )- piperazinyl	4-pyridyl	CN
Ph	Ph-4- morpholinyl	4-pyridyl	CN
Ph	Ph-2-Cl	4-pyridyl	CN
Ph	Ph-3-Cl	4-pyridyl	COMe
Ph	Ph-4-CF <sub>3</sub>	4-pyridyl	SO <sub>2</sub> Me
Ph	Ph-4-S-Me	4-pyridyl	CN
Ph	Ph-4-S(O)- Me	4-pyridyl	CN
Ph-4-F	(4-methyl)- 2-thiophenyl	4-pyridyl	CN
Ph-4-F	(3-methyl)- 2- thiophenyl	4-pyridyl	COMe
Ph-4-F	(4-bromo)-2- thiophenyl	4-pyridyl	SO <sub>2</sub> Me
Ph-4-F	(5-methyl)- 2- thiophenyl	4-pyridyl	CN
Ph-4-F	Ph-4-F-3-Cl	4-pyridyl	CN
Ph-4-F	2- benzoxazolyl	4-pyridyl	CN
Ph-4-F	2- benzofuranyl	4-pyridyl	CN

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Ph-4-F	4- (O(CH <sub>2</sub> ) <sub>3</sub> N Me <sub>2</sub> )-Ph	4-pyridyl	CN
Ph-4-F	4- (O(CH <sub>2</sub> ) <sub>2</sub> N- piperidinyl)- Ph	4-pyridyl	CN
Ph-4-Cl	Ph-4-F	4-pyridyl	CN
Ph-3-Cl	Ph-4-F	4-pyridyl	CN
Ph-2-Cl	Ph-4-F	4-pyridyl	CN
Ph-3,4-Cl	Ph-4-F	4-pyridyl	CN
Ph-3-CF <sub>3</sub>	Ph-4-F	4-pyridyl	CN
Ph-4-S-Me	Ph-4-F	4-pyridyl	CN
Ph-4-S(O)- Me	Ph-4-F	4-pyridyl	CN
Ph-2-OBn	Ph-4-F	4-pyridyl	CN
Ph-4-Br	Ph-4-F	4-pyridyl	CN
Ph-2-OMe	Ph-4-F	4-pyridyl	CN
Ph-3-OMe	Ph-4-F	4-pyridyl	CN
Ph-4-OMe	Ph-4-F	4-pyridyl	CN
Ph-4-NO <sub>2</sub>	Ph-4-F	4-pyridyl	CN
Ph-4-NMe <sub>2</sub>	Ph-4-F	4-pyridyl	CN
Ph-4-(4-N- COCH <sub>3</sub> )- piperazinyl	Ph-4-F	4-pyridyl	CN
Ph-4- morpholinyl	Ph-4-F	4-pyridyl	CN

12. A method of treating a cytokine mediated disease in a mammalian patient in need of such treatment, which comprises administering to said patient an amount of a compound of claim 1 which  
5 is effective for treating said cytokine mediated disease.

13. The method according to claim 12 wherein the cytokine inhibited is IL-1.



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14. The method according to claim 12 wherein the cytokine inhibited is TNF.
- 5 15. The method according to claim 12 wherein the cytokine inhibited is IL-8.
16. The method according to claim 12 wherein the cytokine mediated disease is septic shock, endotoxic shock, gram  
10 negative sepsis or toxic shock syndrome.
17. The method according to claim 12 wherein the cytokine mediated disease is bone resorption diseases, graft versus host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis,  
15 gout, psoriasis, or topical inflammatory disease states.
18. The method according to claim 12 wherein the cytokine mediated disease is adult respiratory distress syndrome, asthma, or chronic pulmonary inflammatory disease.  
20
19. The method according to claim 12 wherein the cytokine mediated disease is cardiac and renal reperfusion injury, thrombosis or glomerulonephritis.
- 25 20. The method according to claim 12 wherein the cytokine mediated disease is Crohn's disease, ulcerative colitis, or inflammatory bowel disease.
21. The method according to claim 12 wherein the  
30 cytokine mediated disease is cachexia.
22. The method according to claim 12 wherein the cytokine mediated disease is a viral infection.

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23. A method of treating inflammation in a mammalian patient in need of such treatment which comprises administering to said patient an amount of a compound of claim 1 which is effective for treating inflammation.

5

24. A pharmaceutical composition which comprises a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/17324

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 401/04, 403/04; A61K 31/40, 31/44

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/276.4, 167, 277, 118; 548/517, 518; 544/333, 277, 238, 284; 514/252, 256, 266, 343, 314, 259, 303, 422

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	SILVESTRI, G. et al. Electrochemical oxidation of substituted pyrroles. IV. The influence of soluble bases. Journal of Heterocyclic Chemistry. December 1992, Volume 29, pages 1847-1850, see entire document.	1-11 ----- 1-11 ----- 12-24
X --- Y --- A	PETRUSO, S. et al. Electrochemical oxidation of substituted pyrroles. III. Anodic oxidation of 2,5-diphenyl-3-acetylpyrrole. Journal of Heterocyclic Chemistry. April-May 1991, Volume 28, pages 793-796, see entire document.	1-11 ----- 1-11 ----- 12-24
X --- Y --- A	CLERICI, F. et al. Cycloaddition reactions of 3-methyloxazolium-5-olates to 4-arylidene-5(4H)-isoxazolones. Chemische Berichte. 1989, Volume 122, pages 295-300, see entire document.	1-11 ----- 1-11 ----- 12-24

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/117324

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,502,051 A (SCHARFENBERG ET AL.) 26 March 1996, see entire document.	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/I7324

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

546/276.4, 167, 277, 118; 548/517, 518; 544/333, 277, 238, 284; 514/252, 256, 266, 343, 314, 259, 303, 422

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